HETEROCYCLES, Vol. 61, 2003, pp. 593 - 637
Received, 28th July, 2003, Accepted, 8th October, 2003, Published online, 14th October, 2003

MODIFICATION OF MACROCYCLIC COMPOUNDS BY AZAHETEROCYCLES

Nadezhda A. Itsikson, Gennady L. Rusinov, Dmitry G. Beresnev, and Oleg N. Chupakhin

Institute of Organic Synthesis of Russian Academy of Sciences, 620219, Ekaterinburg, Russian Federation, Fax: +7 3432 741189; e-mail: chupakhin@ios.uran.ru

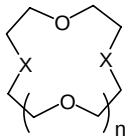
Abstract – Synthesis, modification and properties of macrocycles, such as crown ethers, their open-chain analogues, i.e. podands, calixarenes and resorcinarenes, having azaheterocyclic fragment are discussed**.**

INTRODUCTION

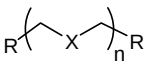
Recently the number of publications dealing with synthesis of self-assembling molecules has been increasingly growing. Of special interest are the compounds having a molecular cavity. They can be used for creation of sensors, high-selective reagents for analytical chemistry.[1-5] To increase the receptor ability and stability of a supramolecule a large surface of "host-guest" interaction and their multicenter binding

are necessary. In this context the introduction of heterocyclic fragments into macrocyclic system is very promising. It results in the coupling of different complexation centers in one molecule, which provides more effective linking "guest"-molecule. The grafting of a heterocyclic moiety leads to change of molecular cavity size and receptor ability of compounds. On the other hand the introduction of lipophilic fragments into pharmacophore heterocycles affects membranotropic properties of obtained compounds and their biological activity.

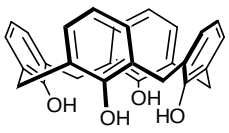
The present review updates the synthetic approaches which are used for derivatization of macrocycles such as crown ethers (**1**), their open-chain analogues, i.e. podands (**2**), calixarenes (**3**) and resorcinarenes (**4**) by azaheterocycles presented in the literature since 1993.



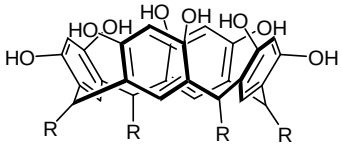
1



2



3

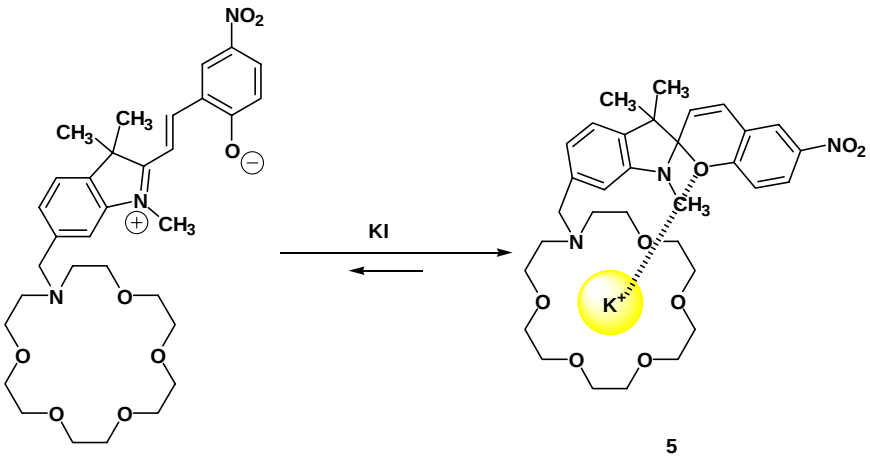


4

1. SYNTHESIS AND BINDING PROPERTIES OF HETARYL-CONTAINING CROWN ETHERS

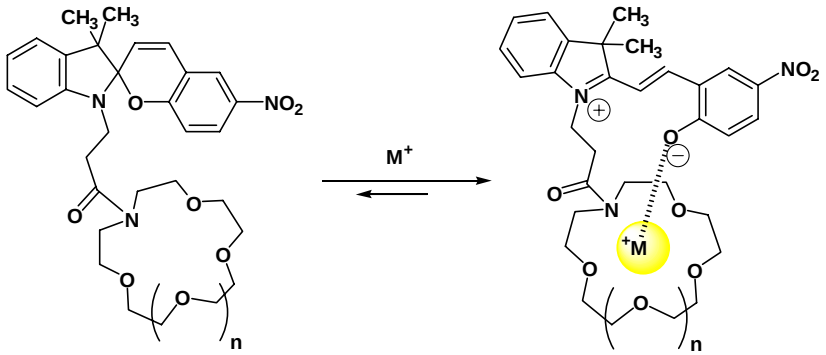
Crown ethers are of great interest due to their high ability to bind spherical substrates such as metal cations or halide ions.[5,6] The basic principle of this interaction is accordance of cavity size with "guest" radius.[1,2] The synthesis of ligands with arrangement of binding centers other than that in the crown ethers provides additional possibility. Thus, ligands having pyridine type nitrogen atom in addition to polyether ring, significantly offered for selective extraction of Ag^+ cation in the presence of K^+, Ba^{2+}, Pb^{2+}.[7-11] Introduction of oligopyridyl-fragments in the crown ethers makes it possible to firmly bind Ru^{3+} cation.[12] Quinazoline derivative appended diaza-18-crown-6 selectively responds to Cd^{2+} over other tested metal ions via a large increase in fluorescence.[13] For recognition of Cu^{2+} cations in the presence of Pb^{2+}, K^+, Zn^{2+}, Cd^{2+} the design of receptor molecules containing redox active 1,2,4-thiadiazole-based fluoroionophores is a promising approach.[14] Heterocycle-containing crown ethers with chiral centers are able to recognize enantiomers of ammonium salts.[15,16] The bis(terpyridyl) bridging ligands containing aza-crown macrocyclic spacer groups have recently been in particular interest for preparation of di- and trinuclear complexes.[17,18] Moreover, the binding of metal ions affects luminescent properties of obtained compound. Thus, e.g., the stable complexes of Re^+ and Ru^{3+} have higher fluorescence as compared with free ligands.[21] The flexible spacer in the molecule allows intramolecularly transfer photoinducted power between metal cation and heterocyclic moiety it as occurs in Ru^{3+} and Os^{3+} complexes of polypyridyl-containing crown ethers. Such compounds can be applied as luminescent and electrochemical sensors and to produce novel polymeric films.[19,20,21] Crown ethers containing photochromic heterocycles (e.g. spirobenzopyrans or thiopyrans) are used for

photoswitch extraction, molecular electronic and transfer through membrane and creation of optical systems. The properties of these compounds have been detailed in the review.[61] The possibility of control of photochemical properties using complexation is illustrated in Scheme 1. Thus, photoisomerism of spirane (**5**) is made difficult in the presence of K^+ cation suitable for the cavity size (Scheme 1). The increase of length of spacer connecting heterocyclic and crown ether fragments makes it possible to form coordination bond between metal cation and phenolate oxygen atom, and to stabilize merocyanine form of spirocompound (**2**) (Scheme 2).



5

Scheme 1



6

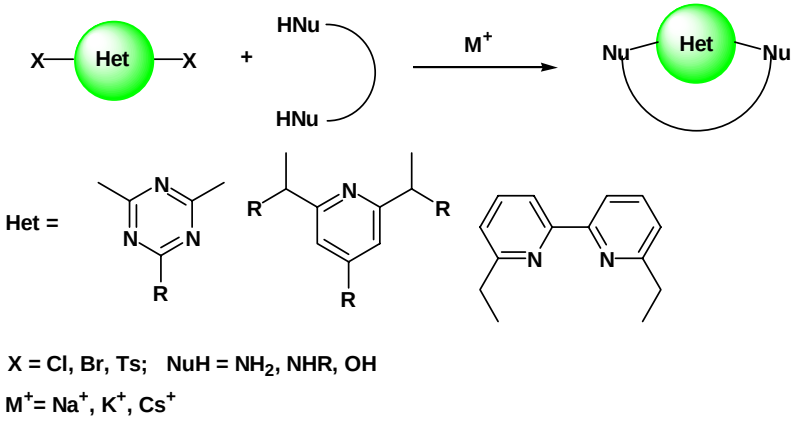
Scheme 2

One cannot but note another useful property of crown ethers, i.e. their high ability to penetrate through biological membrane. Coupling of the lipophilic crown ethers with molecules incorporated into medicinal agents (e.g., indole, benzimidazole, phenothiazine, isoquinoline, pyridine, pyrimidine and triazine derivatives[23]) facilitates the delivery of substance into the cell.

Most of hetaryl-substituted crown ethers described in literature are azacrown ether derivatives. The syntheses of macrocycles containing heterocycle as a sub-cyclic unit, crown ether and benzocrown ether derivatives are rare. The present section focuses mainly on synthetic approaches to the above macrocycles.

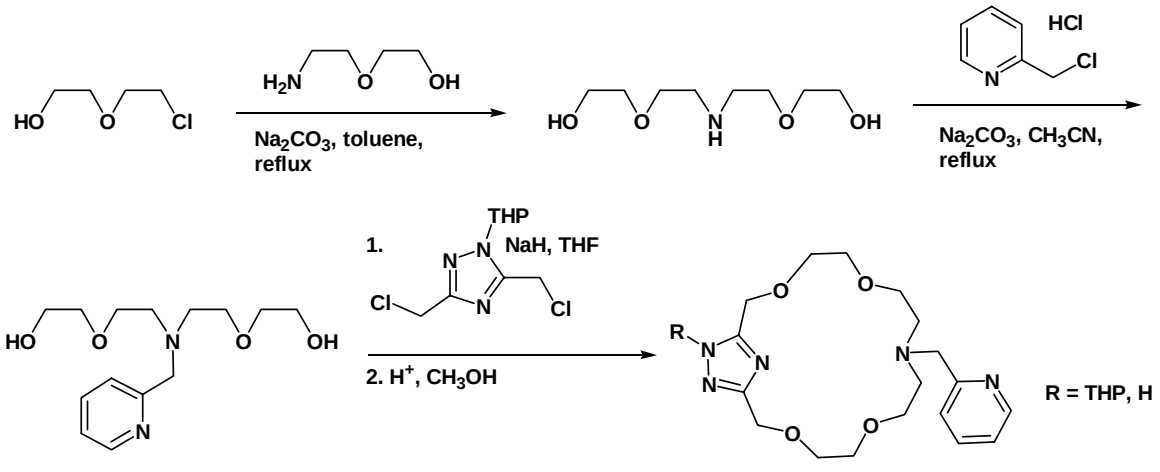
1.1. PREPARATION OF CROWN ETHERS CONTAINING AZAHETEROCYCLES AS SUB-CYCLIC UNIT

A common method for preparation of crown ethers having heterocycle as a sub-cyclic unit is template synthesis based on the nucleophilic substitution reaction. Thus, cyclization of heterocycles containing good leaving groups with binucleophiles gives the pyridyl-,[16,24-30] *s*-triazinyl-,[31,32] isoquinolyl- and pyrazolylcrown ethers (Scheme 3).[33]

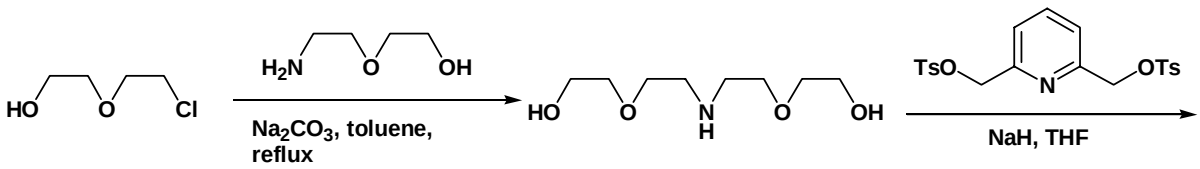


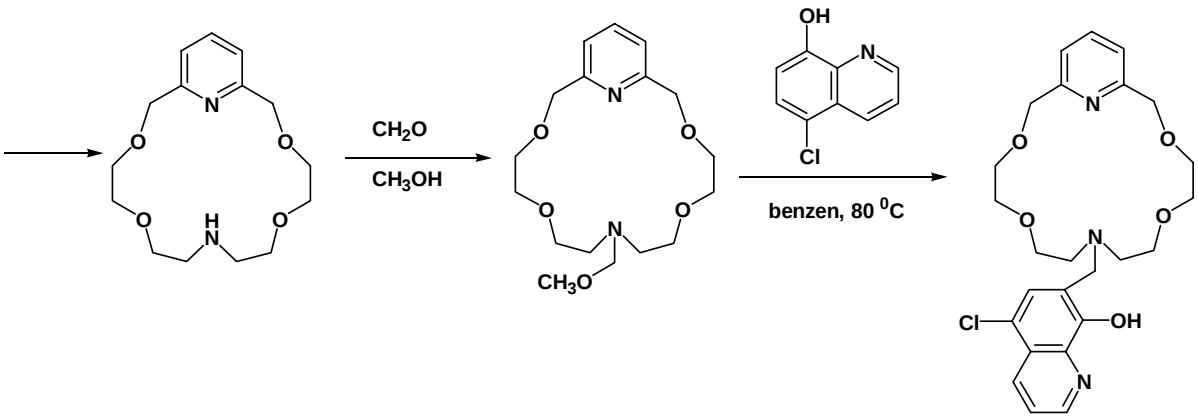
Scheme 3

Additional functional groups in the polyether fragment make it possible to graft other substituents (Scheme 4, Scheme 5).[28]



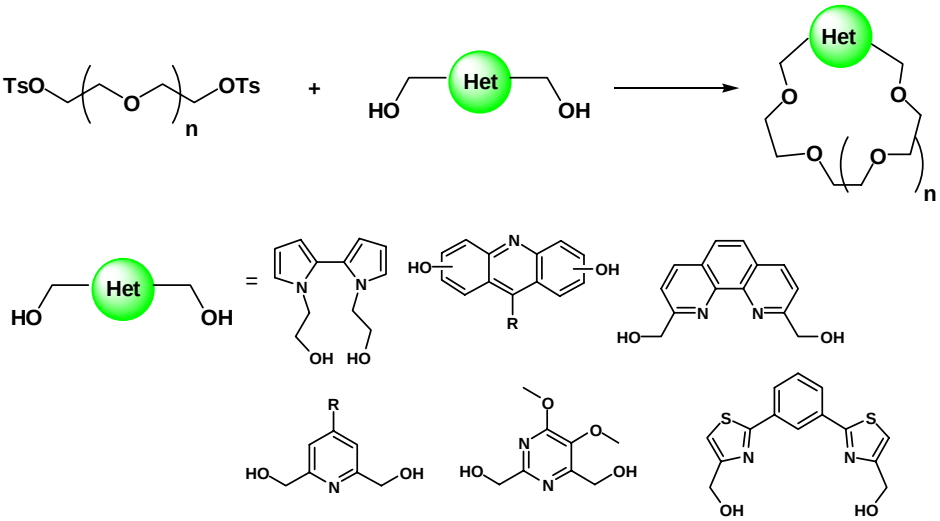
Scheme 4





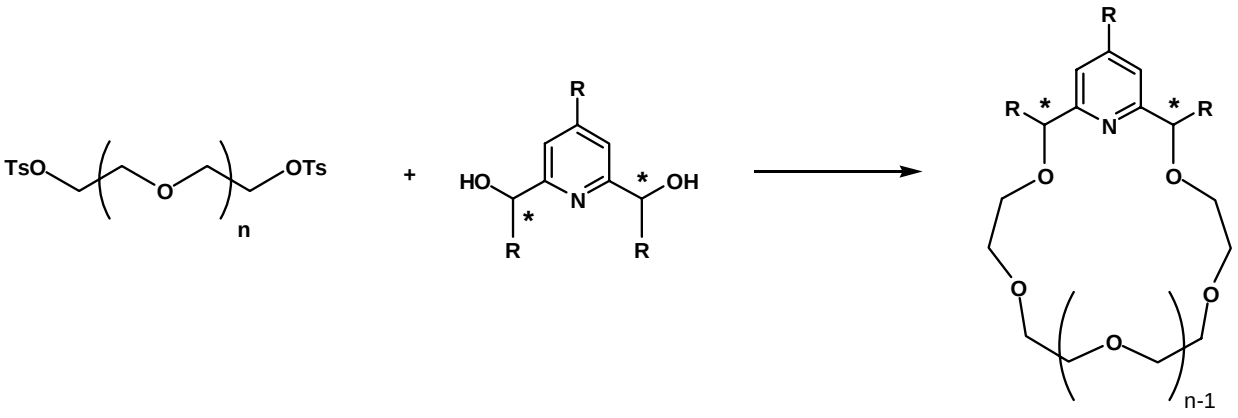
Scheme 5

Crown ether annelated heterocycles were obtained by the reaction of ditosilate(halogen) polyethers with heterocycles containing two nucleophilic groups (Scheme 6).[15,34-39]



Scheme 6

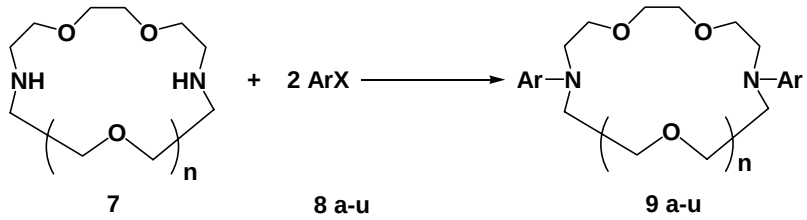
Enantiomeric recognition of amino acids [15,16,39,42] has focused on the interaction of chiral ammonium salts with optically pure crown ethers, prepared as shown in the Scheme 7.[15,16,27,30,39-41]



Scheme 7

1.2. AZACROWN ETHER DERIVATIVES

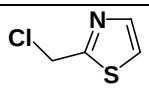
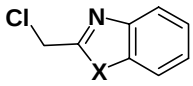
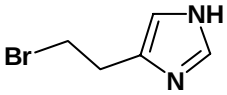
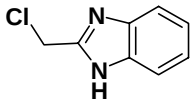
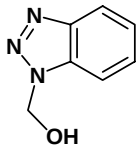
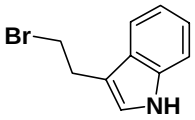
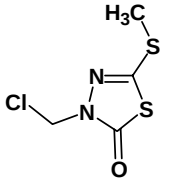
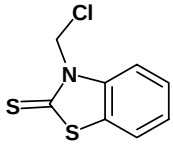
Most of described methods for functionalization of azacrown ethers are nucleophilic substitution at sp^3-hybridized carbon atom. The secondary amino group plays the part of nucleophile and gives access to compounds in which macrocyclic and heterocyclic fragments are bound by flexible spacers of different length. The main advantage of this approach is high yield of target products (Scheme 8, Table 1).

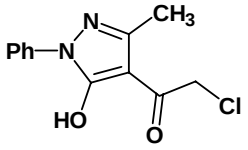
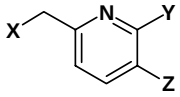
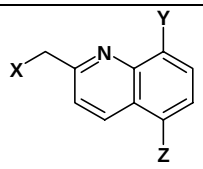
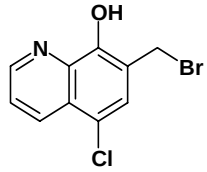
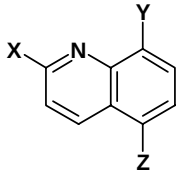
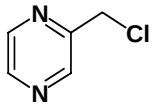
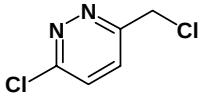
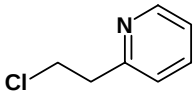
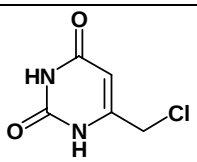


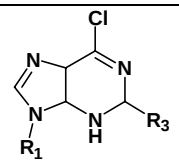
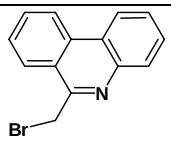
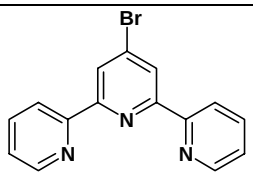
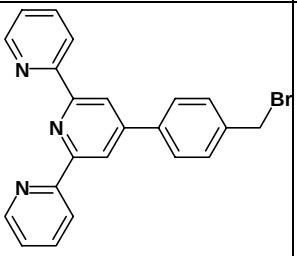
7 **8 a-u** **9 a-u**

Scheme 8

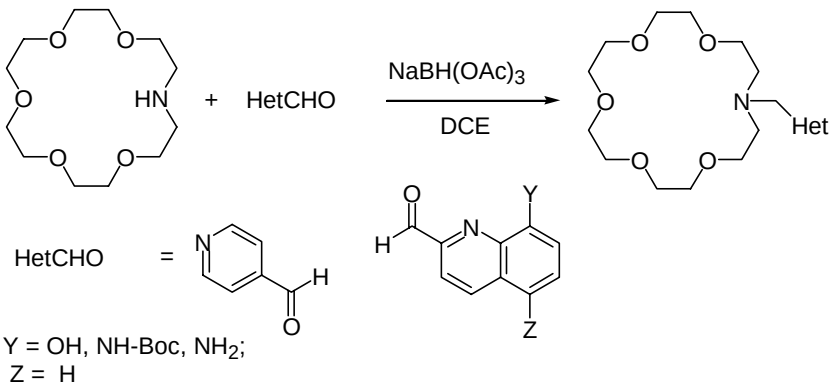
Table 1 Reaction conditions and yields of compounds **9 a-u**

No	ArX (8 a-u)	n	Reaction conditions	(9 a-u), %	Ref.
a		1, 2	8 Kbar, $(C_2H_5)_3N$, THF, 100 ^{0}C, 4-5 days	51-94	9
b	 X= a) S, b) O	1, 2	8 Kbar, $(C_2H_5)_3N$, THF, 100 ^{0}C, 4 days	a) 74-100 b) 64-95	9
c		2	CH_3CN, 82 ^{0}C, 16 h	57	43
d		2	CH_3CN, 82 ^{0}C	60	44
e		2	*i*-C_3H_7OH, 50 ^{0}C, 0.5 - 1 h	91	45
f		2	Na_2CO_3, KI, CH_3CN, Δ	40	46
g		2	$NaBH(OAc)_3$	43	44
h		2	$NaBH(OAc)_3$	39	44

No	ArX (8 a-u)	n	Reaction conditions	(9 a-u), %	Ref.
i		2	$(C_2H_5)_3N$, C_2H_5OH, Δ, 12 h	51	47
j	 a) X = Cl; Y = H; Z = NO_2, CF_3 b) X = Br; Y = H, $CH_2OCH_2OCH_3$, Py, pyrazinyl; Z = H c) X = Br; Y = H, Py; Z = H	a)1,2 b) 2 c) 1,2	a) 8 Kbar, $(C_2H_5)_3N$, THF, 100 ^{0}C, 3-5 days b) C_2H_5OH, 70 ^{0}C, 1-2 h c) 8Kbar, $(C_2H_5)_3N$, THF, 100 ^{0}C, 4 days	a) 77-95 b) 63-94 c) 51-93	9 10 48
k	 a) X = Br; Y = OMe, OH; Z =Cl b) X = Br, Y = NO_2; Z = H	2	a) Na_2CO_3, CH_3CN, 80 ^{0}C b) $(C_2H_5)_3N$, benzene, Δ	a) 58-82 b) 90	28 49
l		2	Na_2CO_3, CH_3CN, 80 ^{0}C	63-90	28 13
m	 a) X = H, OH; Y = OH; Z =Cl, NO_2, H, Me b) X = CHO, Y = OH, NH-Boc, NH_2; Z = H	2	a) $(CH_2O)_n$, toluene b) $NaBH(OAc)_3$, DCE	a) 24-85 b) 75-85	50 49
n		1, 2	8 Kbar, $(C_2H_5)_3N$, THF, 100 ^{0}C, 3-4 days	82-90	9
o		1, 2	8 Kbar, $(C_2H_5)_3N$, THF, 100 ^{0}C, 3-4 days	80-81	9
p		1, 2	8 Kbar, $(C_2H_5)_3N$, THF, 100 ^{0}C, 3-4 days	90-93	9
q		2	$NaBH(OAc)_3$	80	44

No	ArX (8 a-u)	n	Reaction conditions	(9 a-u), %	Ref.
r	 R_1 = H, Cl R_3 = H, CH_3, CH_2Ph	2	C_2H_5OH, 8 Kbar, 160 ^0C	41-69	51 52
s			$N(C_2H_5)_3$, THF	52	53
t		2	N_2, 190 ^0C, 20 h	47	54
u		2	1) $NC_2H_5(i\text{-}C_3H_7)_2$, C_2H_5OH, Δ, 1.5 h 2) C_2H_5OH, Δ, 24 h	60 50	17, 54, 55

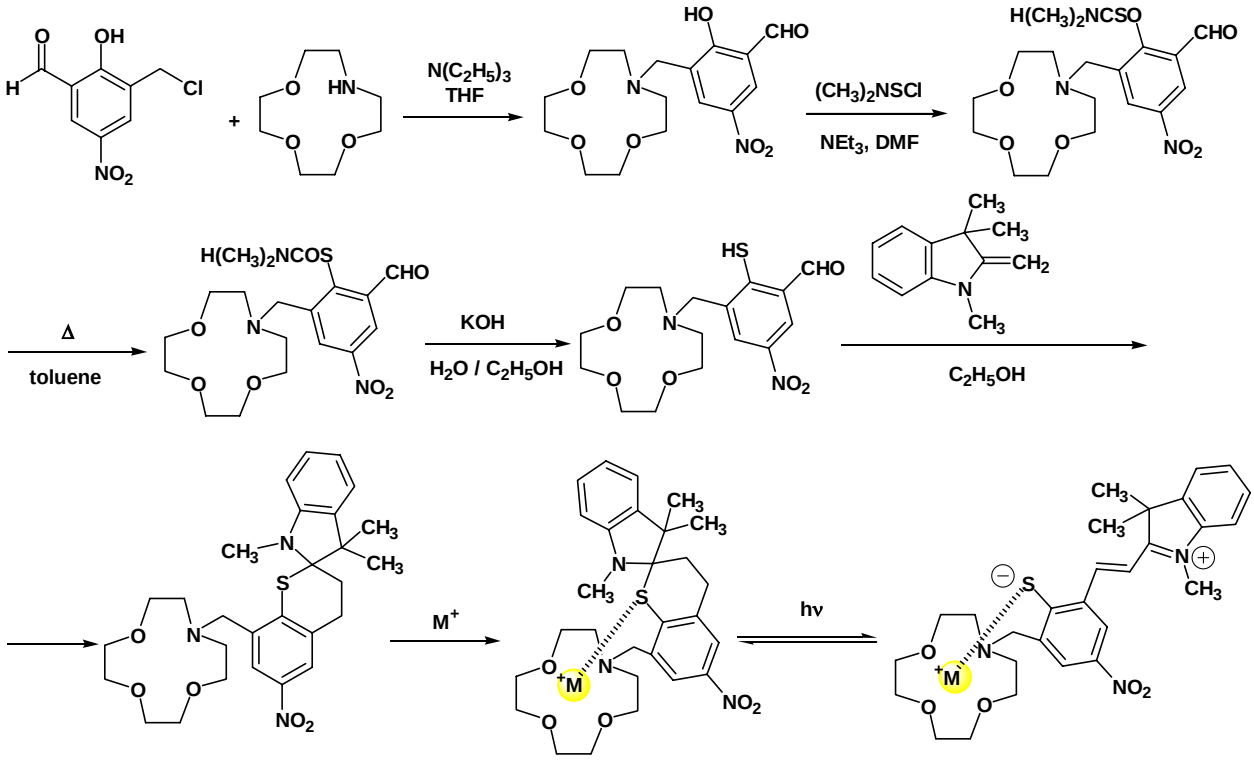
The products similar to **9** were obtained starting from the monoazacrown ethers[10,14,48,54] and diazathiocrown ethers.[10] Sometimes generation of a leaving group occurs in situ. For example, reductive amination of monoaza-15-crown-4 by 4-pyridine- or quinolinecarbaldehyde in the presence of sodium borohydride triacetate results in the pyridyne- and quinoline-substituted azacrown ethers (Scheme 9).[11,49,50] In this case hydroxy group of methylol derivative of heterocycle formed by reduction of formyl function is displaced by action of azacrown ether.



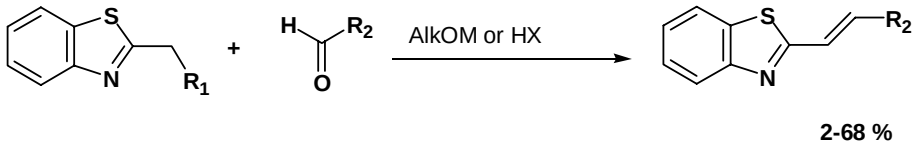
Scheme 9

Nucleophilic properties of azacrown ether were used for the synthesis of ligands containing photochromic heterocycles.[56-59]

As a rule the preparation of these compounds is multistage process. The reaction with heterocyle was proceeded by introduction of functional substituent containing carbonyl (Scheme 10). Formyl group is involved in the condensation affording the formation of photochromic ligands (Scheme 10, Scheme 11).[62]



Scheme 10



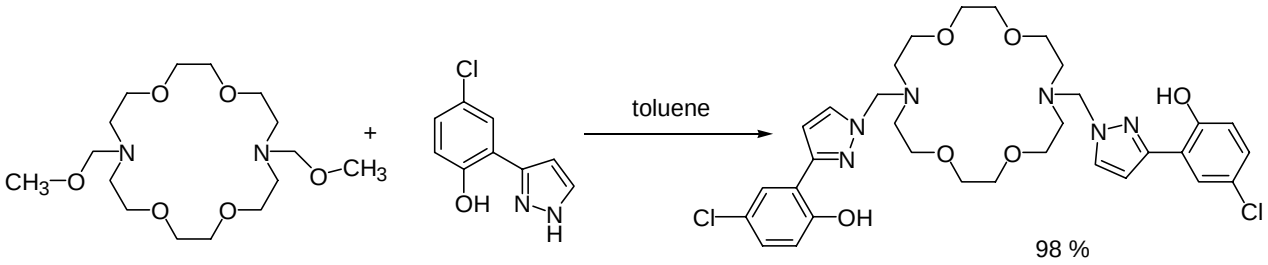
R_1 = H, $P^+Ph_3Br^-$

R_2 =

n = 1,2

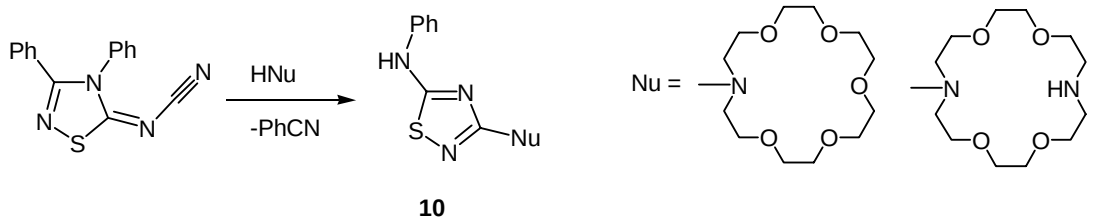
Scheme 11

In rare cases the azacrown derivatives take part in the reaction with azaheterocycles as an electrophilic component. Thus synthesis of dipyrazolyldiazacrown ethers demonstrates that hetaryl-containing azacrown ethers can be obtained by the reaction of substitution of nucleophuge contained in the crown.[50] (Scheme 12)



Scheme 12

Azacrown ethers directly linked with heterocycle can be prepared by heterocycle transformation initiated by nucleophilic attack. For example, thiadiazole-containing azacrown ethers (**10**) were obtained by Boulton-Katritzky rearrangement.[56] (Scheme 13)



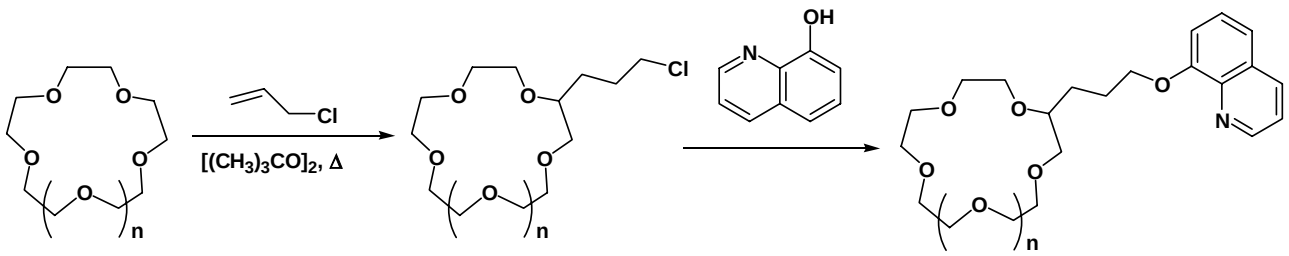
10

Scheme 13

In this case the action of nucleophile leads to the ring opening followed recyclization accompanied by elimination of benzonitrile.

1.3. CROWN ETHER DERIVATIVES

Since the main method for functionalization of crown ethers similar to that for azaanlogues is the nucleophilic substitution of good leaving groups such as halogen, alcoxy, amino etc., the preliminary modification of crown ethers is required for preparing nucleofuge-containing crown ethers. Such functionalization is possible in homolytical displacement of methylene fragment adjacent to oxygen atom. For instance, the addition of radical obtained from the crown ether in the presence of organic peroxide to the double bond of 3-chloropropene results in 3-chloropropylcrown ether (Scheme 14).[63]

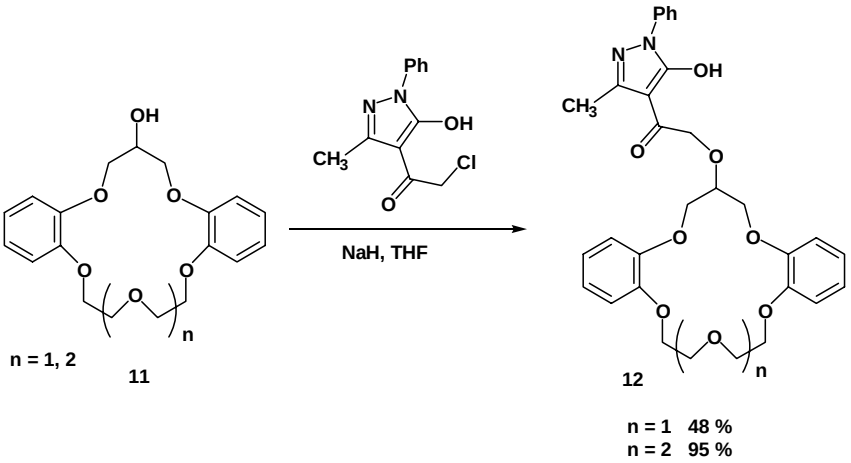


Scheme 14

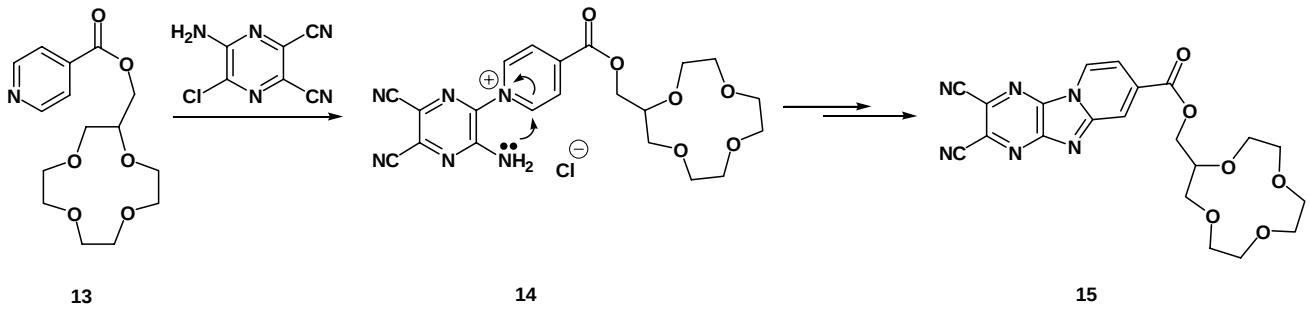
Homolytical hydroxylation of crown ethers makes it possible to introduce nucleophilic function into the crown which will be used for further interaction with heterocycle. The reaction of hydroxy-substituted

crown ethers 7 with chloro-derivatives of pyrazole affords product (**12**) in which heterocyclic and macrocyclic moieties are bound by a flexible spacer (Scheme 15).[47]

An interest example of heterocycle building has been described in the papers.[64-66] Crown-containing isonicotinate (**13**) reacts with 2-amino-3-chloro-5,6-dicyanopyrazine to give pyridinium salt (**11**) with further intramolecular cyclization including reaction of nucleophilic substitution of hydrogen (S_N^H-process) at unsubstituted carbon atom of activated pyridine, which results in the formation of pyrido[1',2':1,2]imidazo[4,5-*b*]pyrazine-containing crown ether (**15**) (Scheme 16).



Scheme 15

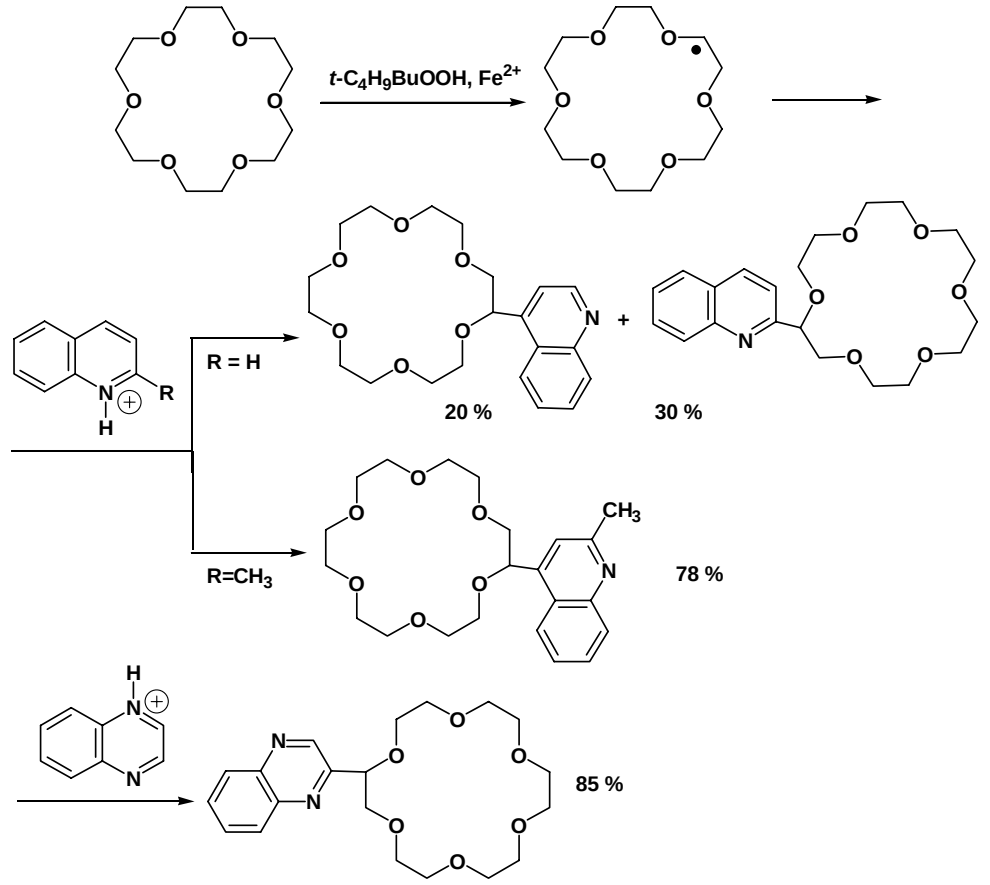


Scheme 16

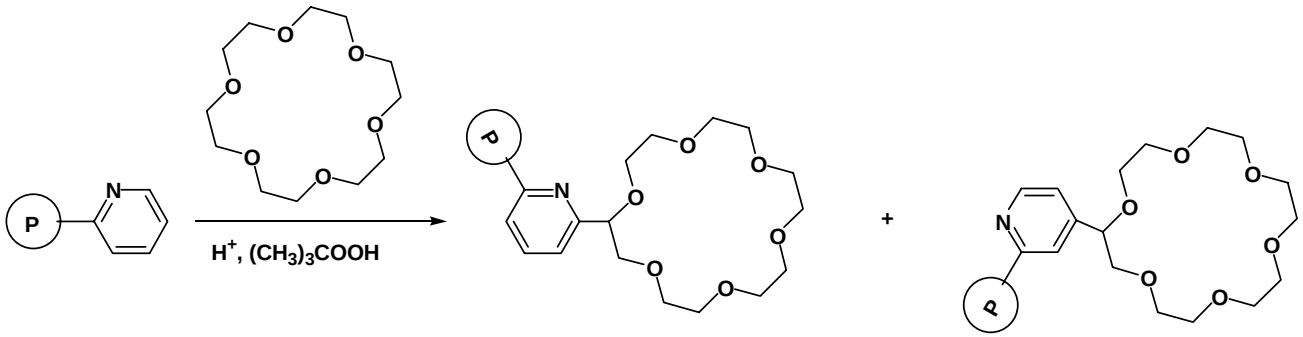
Direct C-C bond formation seems undoubtedly promising. The only case of immediate coupling of crown ether with heterocycles is homolytical hetarylation by 2-substituted quinolines and quinoxaline (Minisci procedure). The reaction of nucleophilic radical initiated at the first stage with NH-salts of quinoline and quinoxaline results in the formation of aromatic products in which heterocyclic and crown ether fragments are linked by C-C bond (Scheme 17).[67,68]

One-stage grafting of crown ethers to copolymer of vinylpyridine with styrole is based on the method of homolytic hetarylation (Scheme 18).[69] Crown ether-containing polymers substantially simplify phase transfer catalysis while showing reactivity compared with that of active catalysts of low temperature processes.

The traditional method for template synthesis of macrocycles with the participation of heteryl-containing synthons is also suitable for preparing heterocycle-containing crown ethers. Thus, condensation of hydroxyalkyl derivative of heterocycles with polyethylene glycol ditosylates is a convenient one-stage method for combination of heterocyclic and crown ether fragments in a molecule.[51,70] Using this approach makes it possible to form macrocyclic analogues of natural nucleosides such as crown-containing purines (**16**) and (**17**) in which crown moiety can be bound both with azine and azole fragments (Scheme 19).

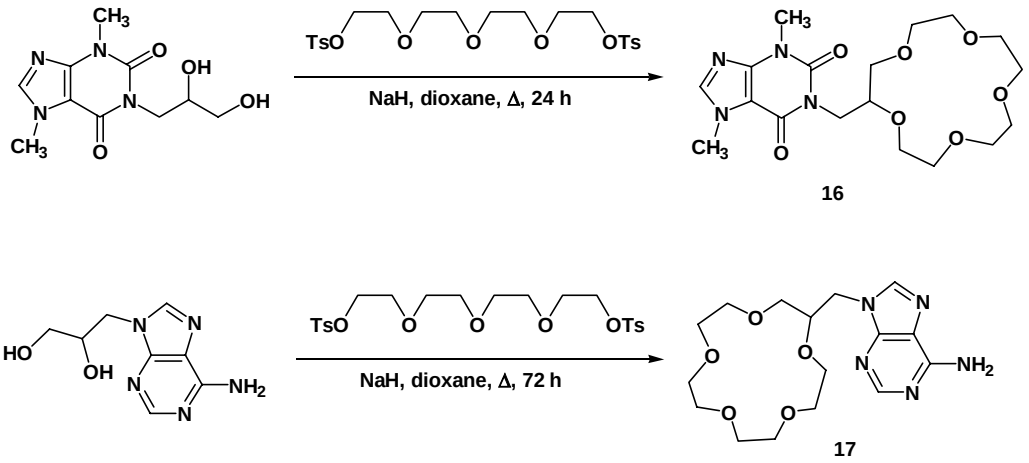


Scheme 17



P = Polymer matrix

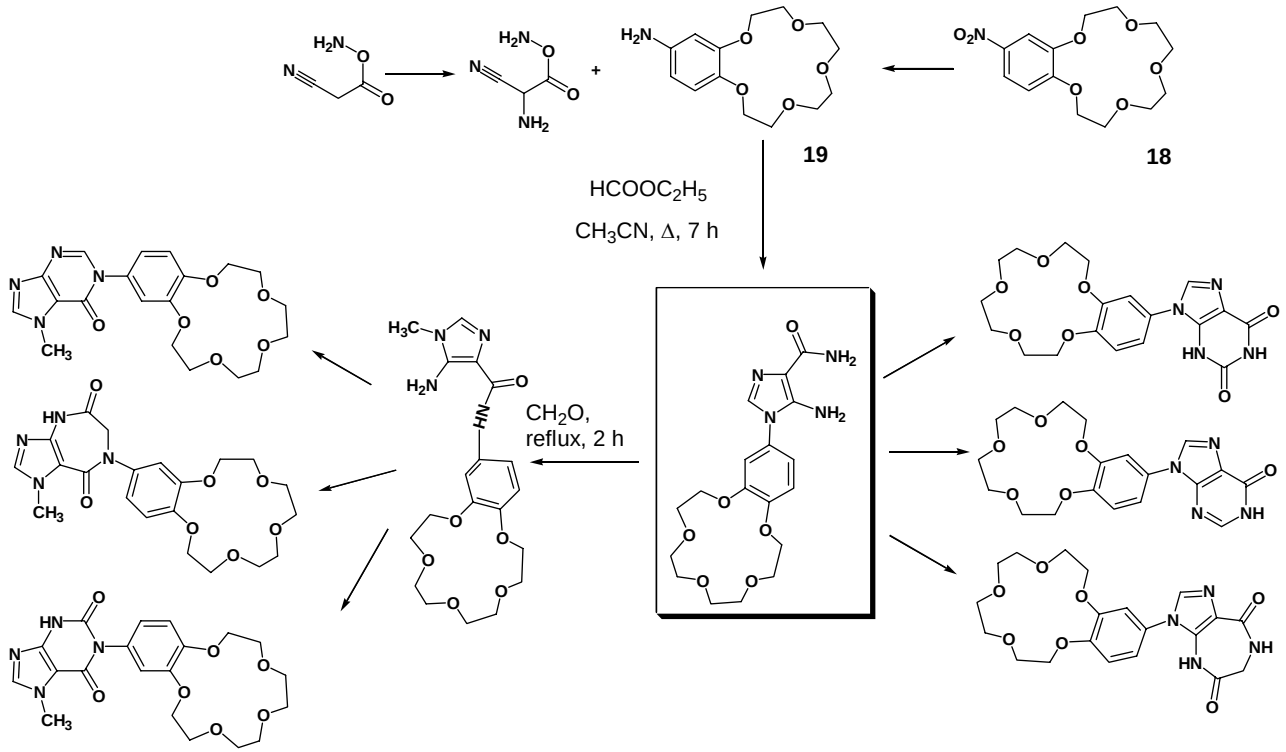
Scheme 18



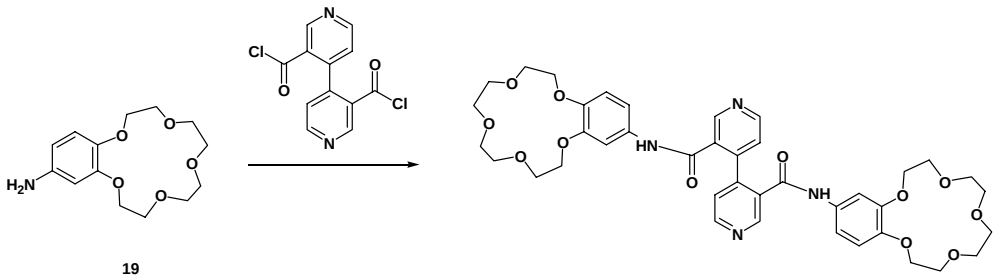
Scheme 19

1.4. BENZOCROWN ETHER DERIVATIVES

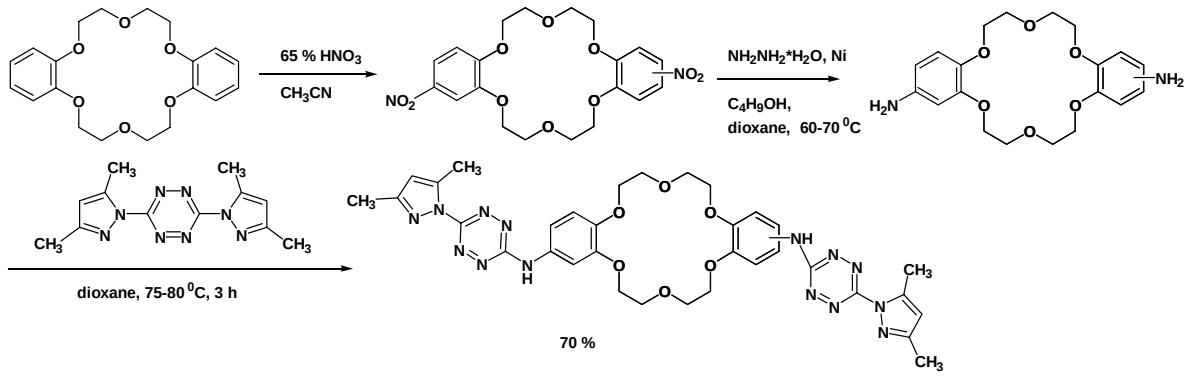
Benzoannelated crown ethers are subjected to electrophilic substitution reactions typical for aromatic compounds (nitration, halogenation, acylation). The products obtained in the $S_E(Ar)$ reactions are convenient starting materials for successive building heterocyclic substituent on the crown ether die. Now such approach is the main method. Thus, reduction of nitrobenzocrown ethers (**18**) results in amino derivatives (**19**) which can participate in the reaction of nucleophilic substitution as nucleophiles (Scheme 20, 21, 22).[71-74]



Scheme 20

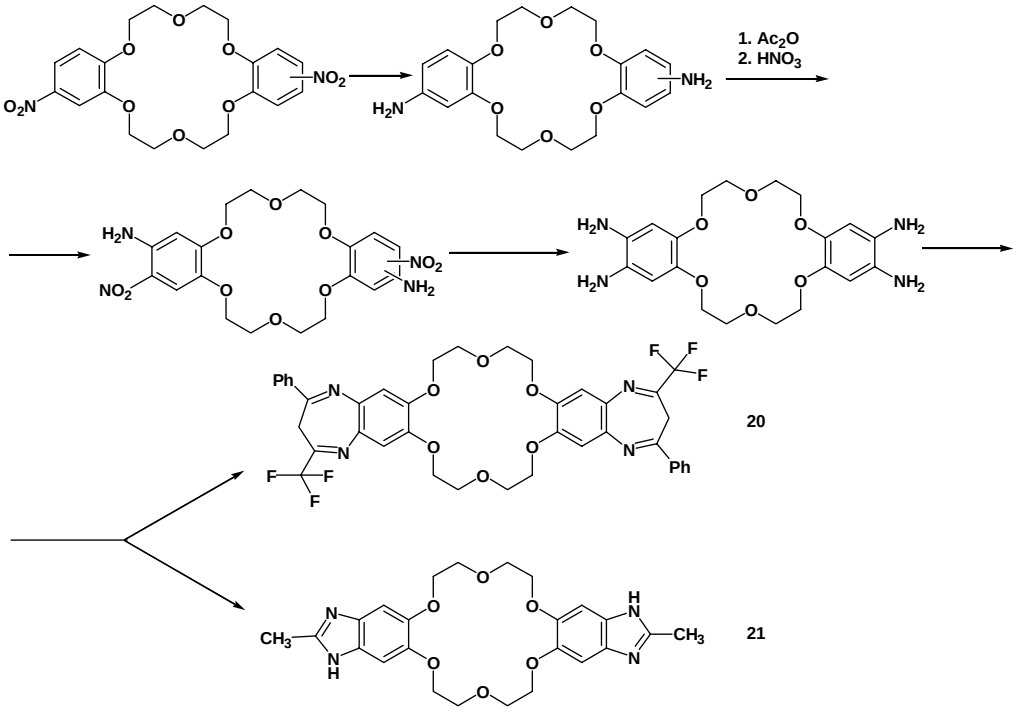


Scheme 21



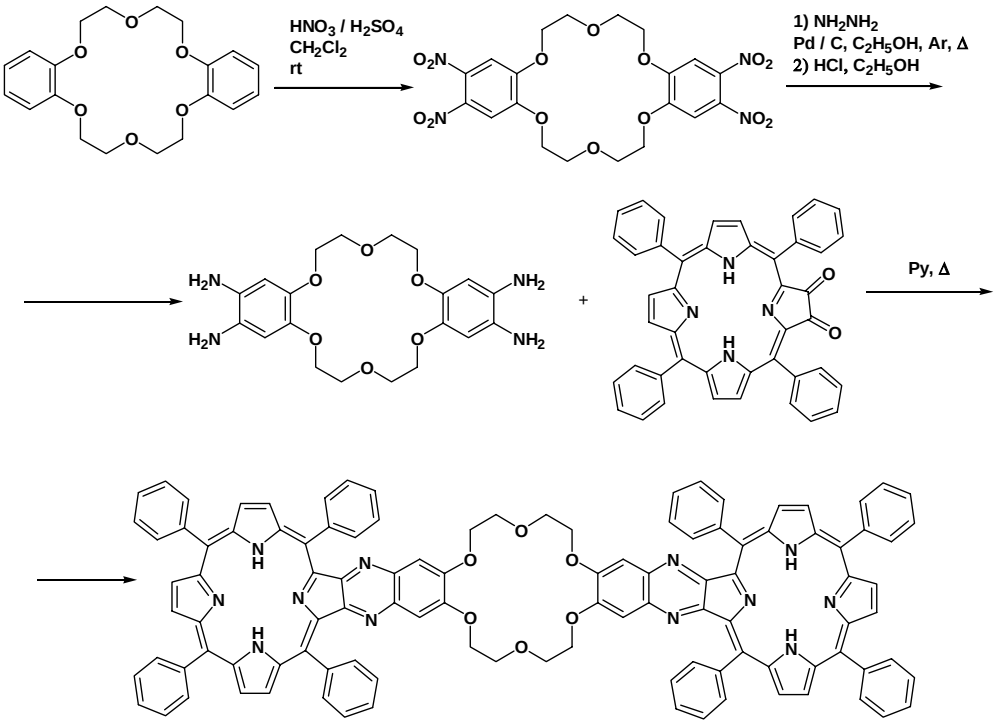
Scheme 22

The introduction of the second amino group into aromatic ring of benzocrown ether allows synthesize their derivatives annelated by benzodiazepine and benzimidazole rings (**20**) and (**21**), respectively (Scheme 23).[71]



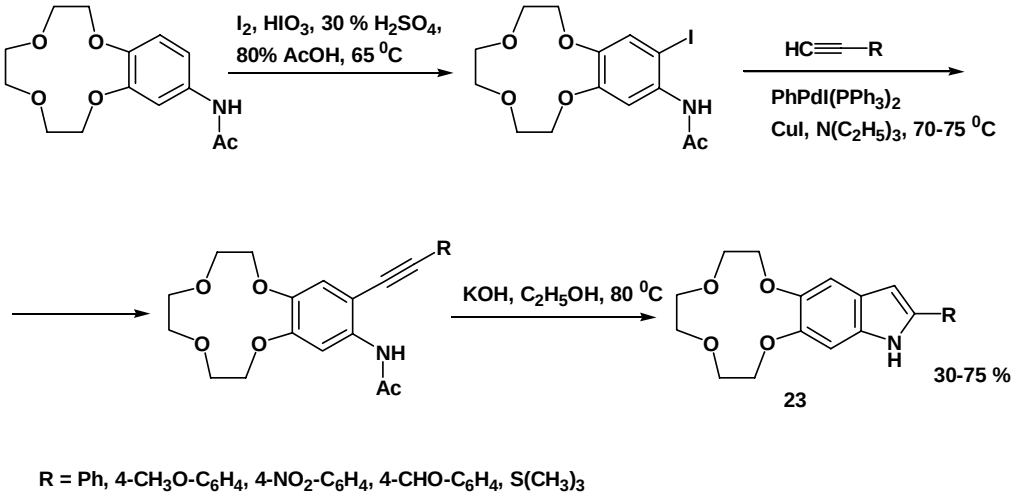
Scheme 23

Crownlinked porphirines (**22**) can be obtained from tetraaminodibenzocrown ether in a similar way (Scheme 24).[75]



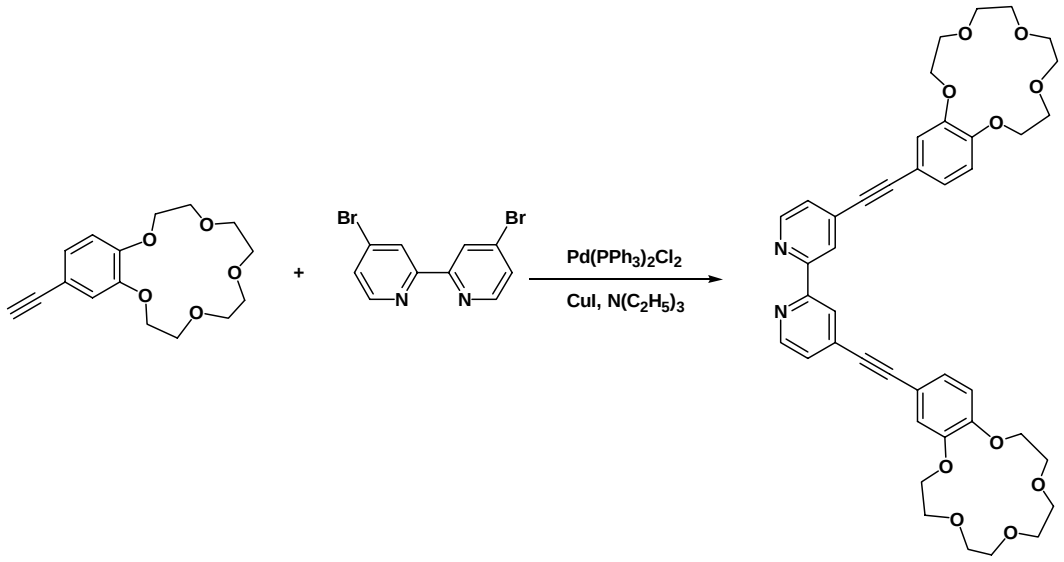
Scheme 24

Iodobenzocrown ethers readily take part in Heck reaction. Intramolecular cyclization of acetylene derivatives prepared using this approach affords indoloannelated crown ethers (**23**) (Scheme 25).[76]



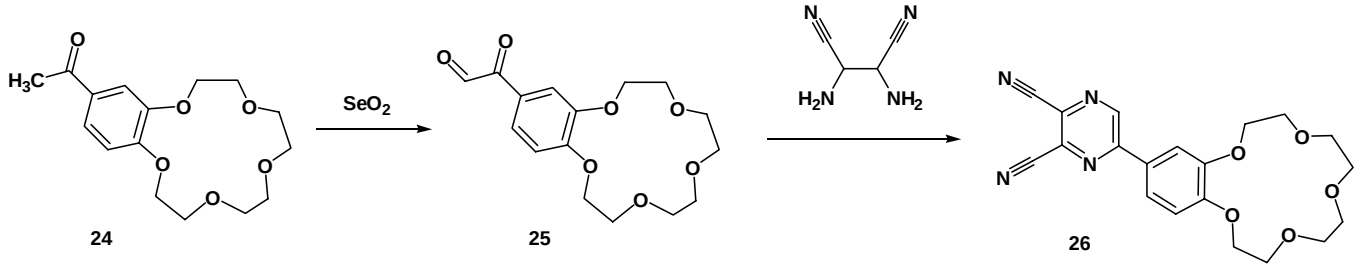
Scheme 25

Cross-coupling of ethynylbenzocrown ethers with bipyridiles can be related to this type of the reactions (Scheme 26).[77]



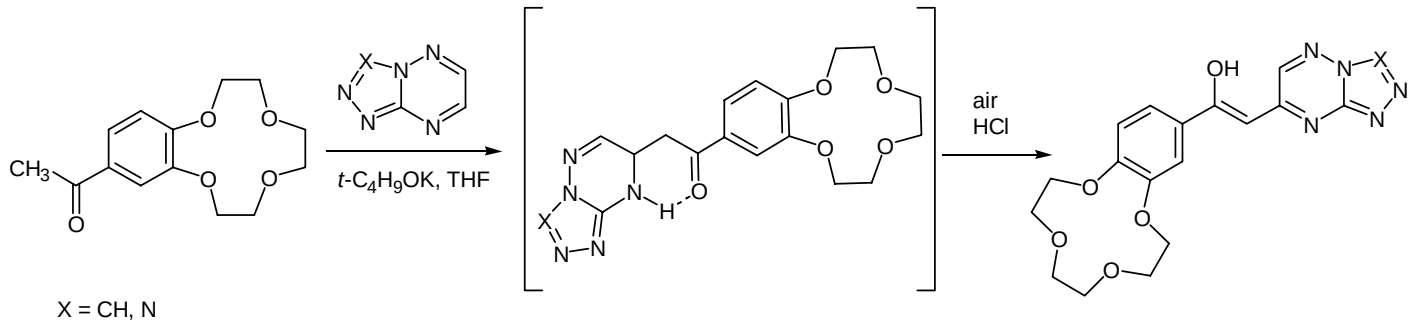
Scheme 26

Introduction of carbonyl group in the aromatic ring opens wide possibility for building heteryl-containing benzoannelated crown ethers. Thus, e.g., oxidation of 4-acetylbenzocrown ether affords the formation of important building block (**25**)**,** based on which different heterocycles can be obtained (Scheme 27).[78]



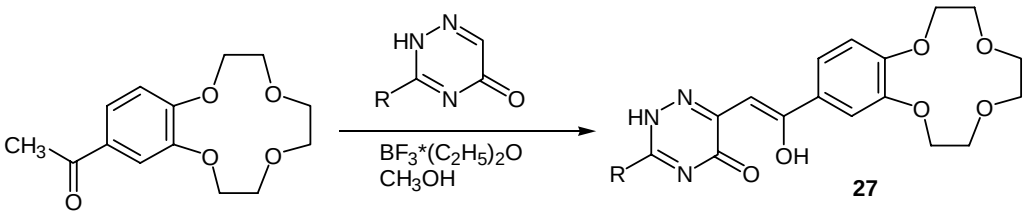
Scheme 27

Product (**26**) might be achieved by nucleophilic substitution in pyrazine ring and reductive decyanation.[79,80] 4-Acetylbenzoannelated crown ethers (**24**) easily react with azoloannelated 1,2,4-triazines and 3-substituted 1,2,4-triazin-5(2*H*)-ones. It has been shown that at the room temperature the interaction of azolotriazines with 4-acetylbenzo-12-crown-4 in the presence of equimolar amount of potassium tert-butoxide results in the extremely smooth oxidative S_N^H-reaction (Scheme 28).[81]



Scheme 28

4-Acetylbenzocrown ethers react with 3-R-1,2,4-traizin-5(2*H*)-ones in the similar manner, being formed within one stage S_N^H-products (**27**) (Scheme 29).[81]



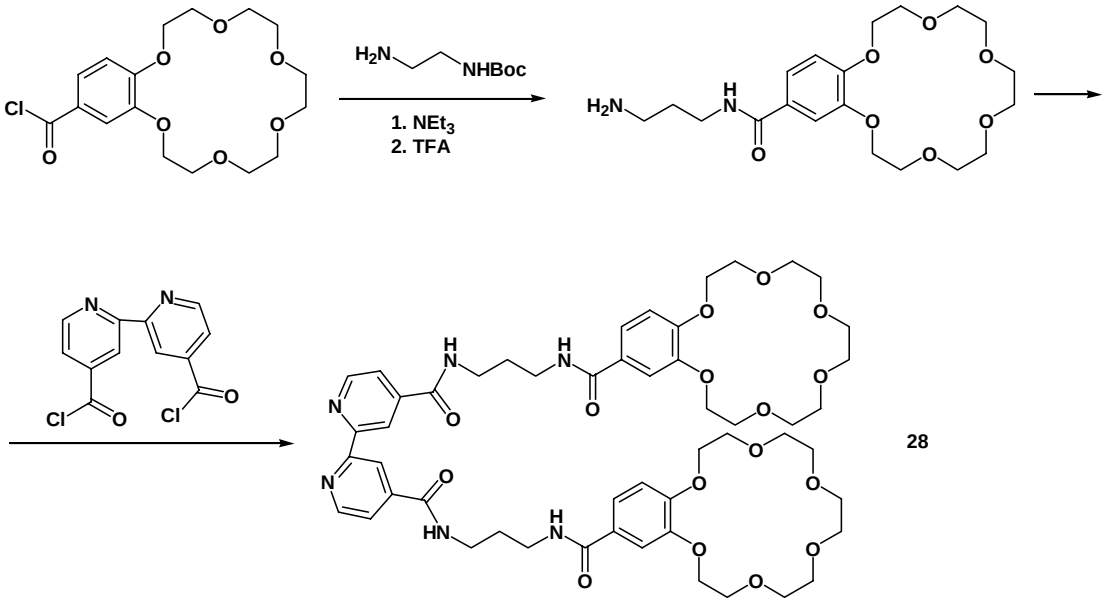
R = Ph, 4-$CH_3C_6H_4$, 4-Cl-C_6H_4, 2-Py

Scheme 29

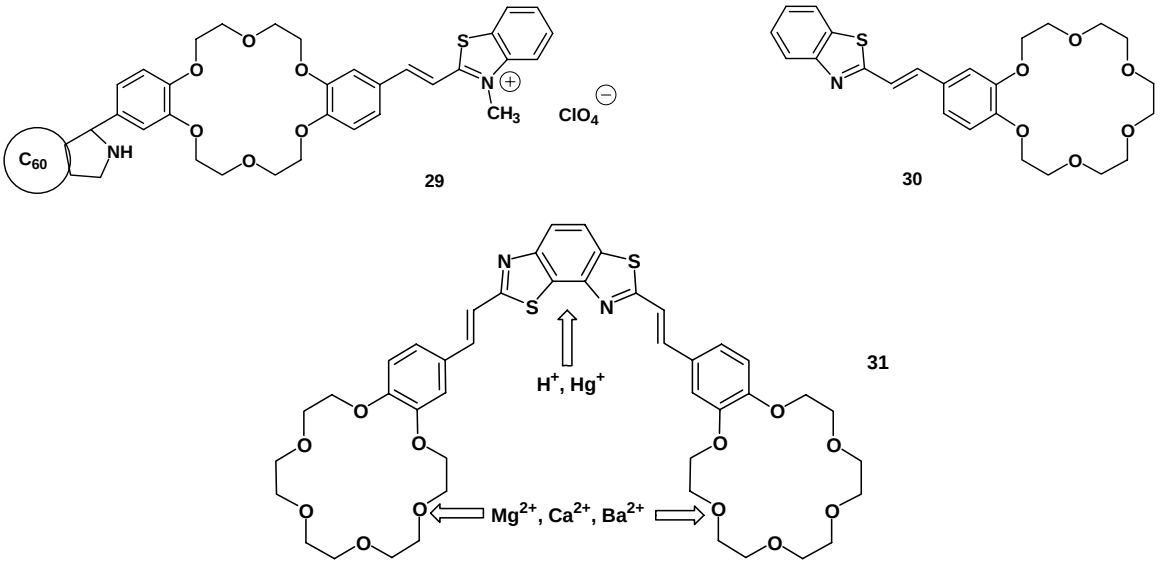
Introduction of COCl group in the aromatic ring of benzocrown ether makes it possible to form the products (**28**) with crown ether fragment by the nucleophilic substitution reaction at one stage (Scheme 30).[73,82]

Formyl group also opens the wide ways to synthesize chromogenic styryl derivatives of crown ethers by the condensation reaction. Using this method a number of structures containing benzothiazole substituent such as styrylbenzthiazoles (**30**),[62] fullerene-containing compounds (**29**)[83] and fluorescent ligands (**31**)[84] were synthesized (Scheme 31).

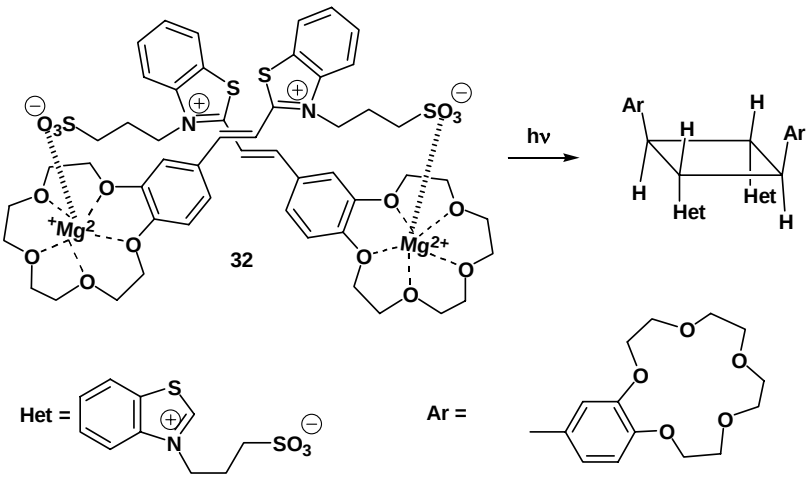
It is interesting to note that crown ether fragment in these compounds affects photochromic properties of heterocycle by complexation. In the presence of Mg^{2+} ions crown-containing styryl dyes give supramolecular dimers with cross-arrangement of molecules.[85] When dimer solutions are photoirradiated the [2+2] cycloaddition proceeds resulting in the only one from 11 possible isomers (Scheme 32).



Scheme 30

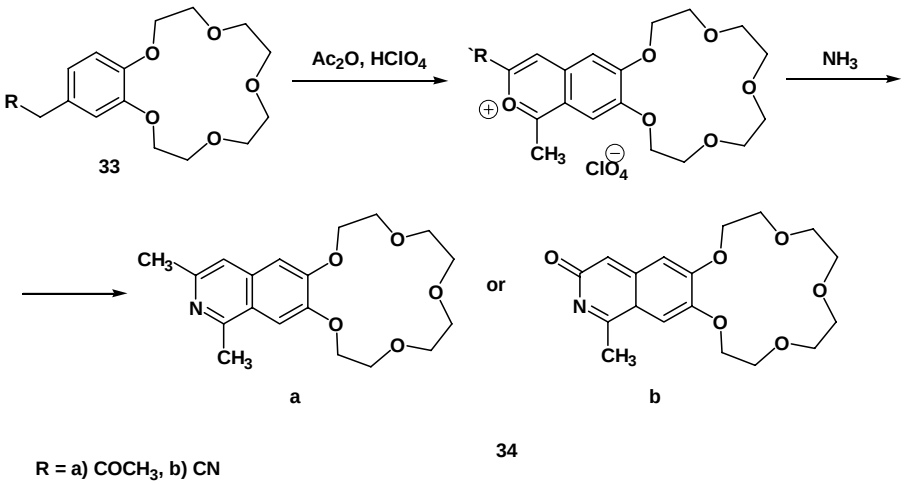


Scheme 31

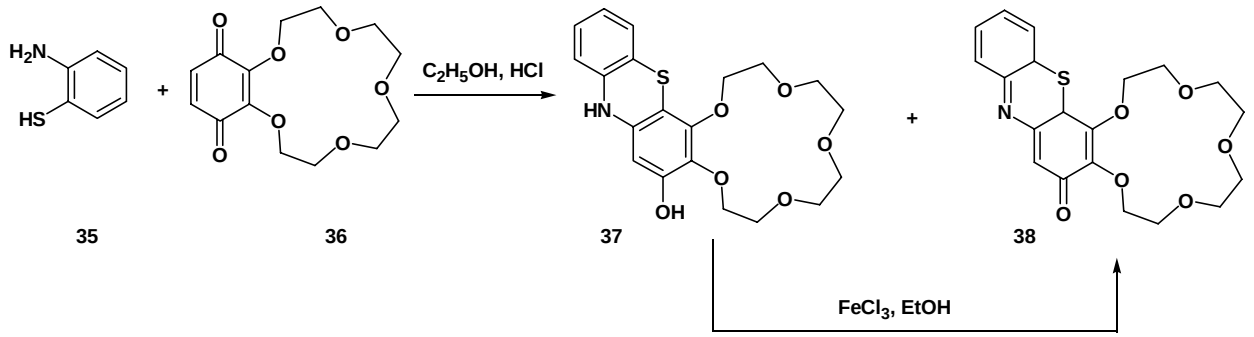


Scheme 32

The reactions of aromatic nuclei in benzocrown ethers are also used for heterocycle annelation. Isoquinolinylcrown ethers (**34**) were obtained from the crown ethers (**33**) *via* the stage of forming crown-2-benzopyryllium salts (Scheme 33).[86]

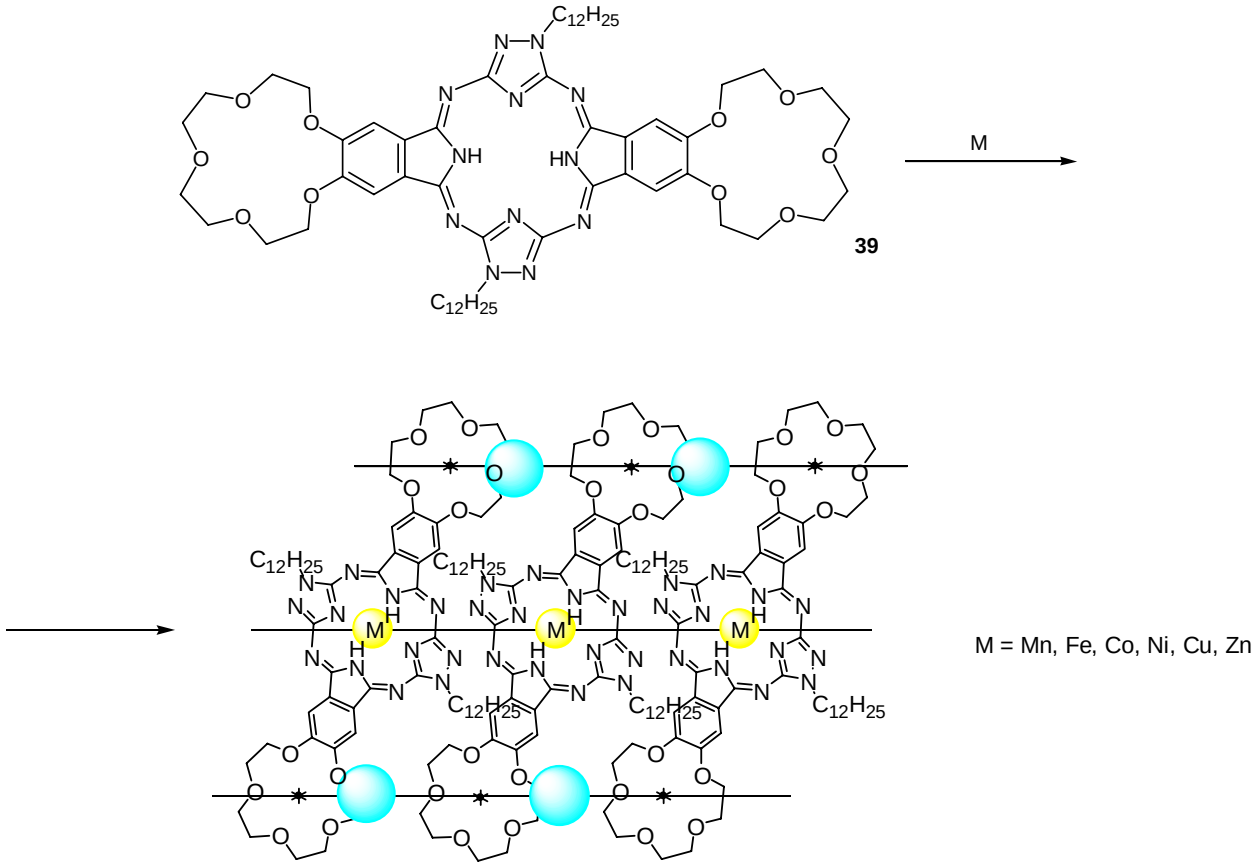


Scheme 33



Scheme 34

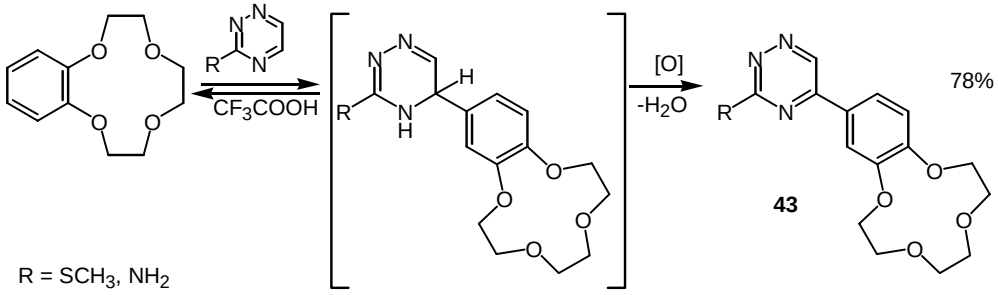
The interaction of 4,5-(3,6,9-thioxaundecandiyldioxy)-1,3-diiminoindoline with 3,5-diamino-1-dodecyl-1,2,4-triazole in ether results in the triazolehemiporphirazine-containing two crown ether fragments (**39**). Such compounds can be used for building ionic channels by Langmuire-Blodgett method (Scheme 35).[88]



Scheme 35

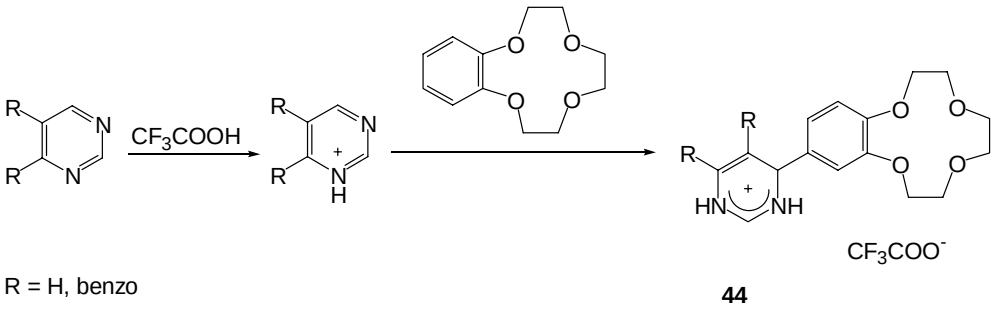
A novel original method for direct C-C coupling of benzocrown ethers with heterocycles has been worked out using 1,2,4-triazine and 1,3-diazines. In the reactions demonstrated in Schemes 36-38 benzoannelated crown ethers were considered as O,O-disubstituted polyphenoles for which reactions with various azines have been studied earlier.[89,90] Such direct C-C coupling can stop at the addition step (compounds (**44**, **45**))

or be completed by formation of compounds (**43**), i.e. products of nucleophilic aromatic substitution of hydrogen (S_N^H –products) which are more stable to protolytical cleavage (Scheme 36).[91,92]



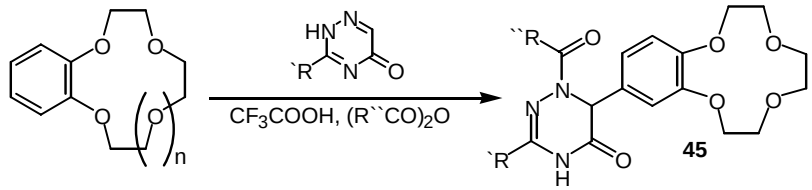
Scheme 36

The use of reaction of nucleophilic addition to unsubstituted carbon atom in azines[93,94] makes it possible to carry out of the interaction of benzoannelated crown ethers with 1,3-diazines in the presence of trifluoroacetic acid results in products (**44**) of nucleophilic addition to unsubstituted C(4)-carbon atom of azine system (Scheme 37).[95]



Scheme 37

The interaction of 1,2,4-traizin-5-ones with benzoannelated crown ethers in the presence of organic anhydrides affords products (**45**) of direct nucleophilic addition to unsubstituted carbon atom of traizine ring (Scheme 38).[96]



R`=Ph , 4-Cl-C_6H_4, *p*-Tol, SC_2H_5, $NHNH_2$
R``=CF_3, CH_3
n = 1, 2, 3

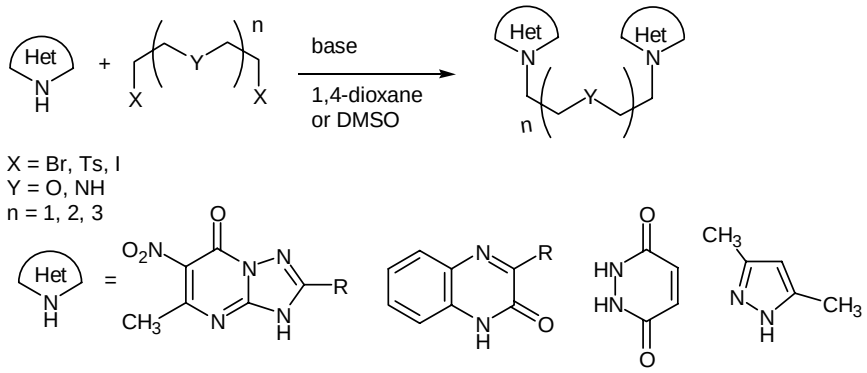
44-92 %

Scheme 38

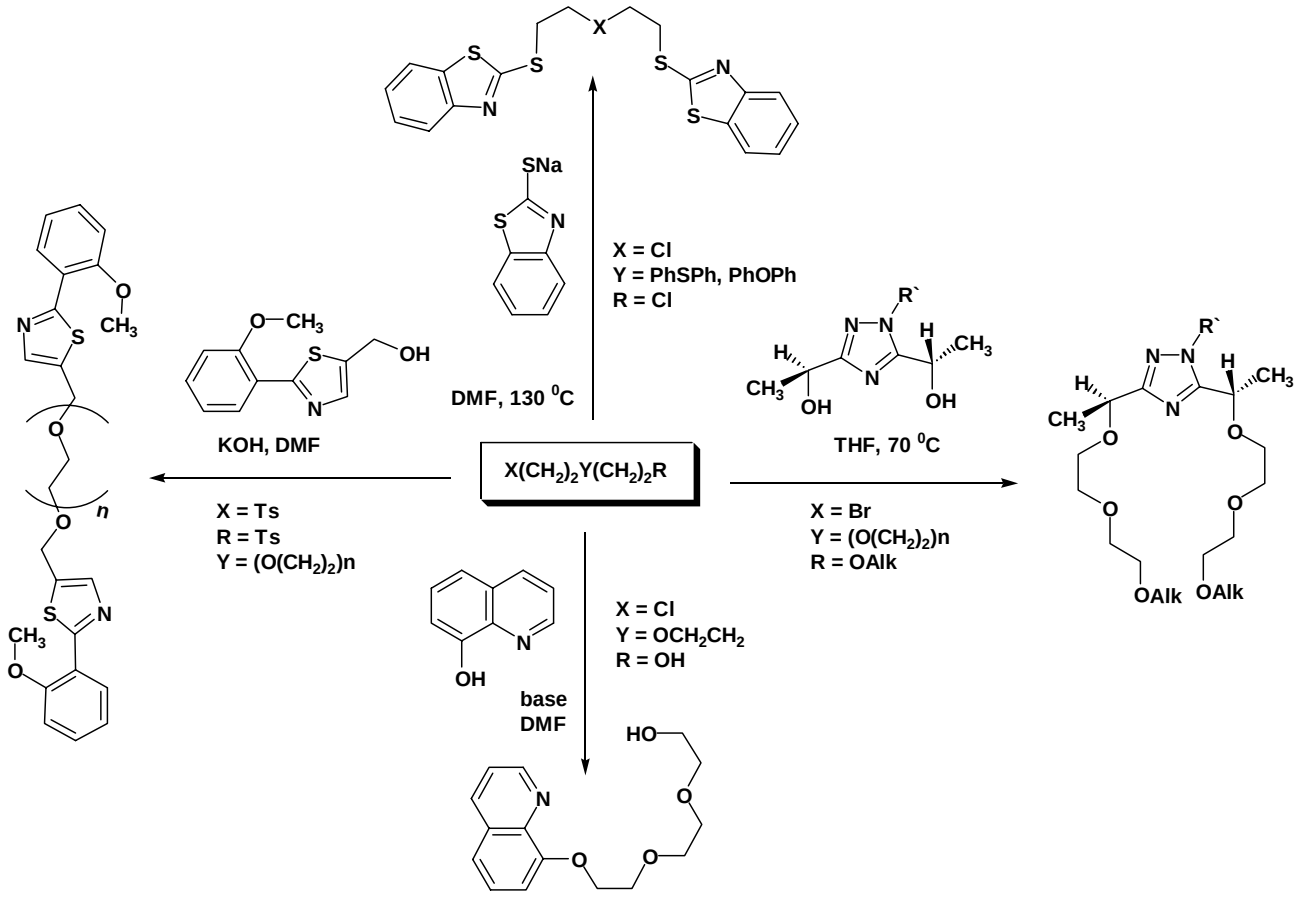
2. MODIFICATION OF OPEN-CHAIN ANALOGUES OF CROWN ETHERS – PODANDS BY AZAHETEROCYCLES

Heteryl-containing podands are of great interest as fluorescent sensors, molecular switchers and compounds for molecular recognition.[97]

The main way for preparing these compounds is the reaction of nucleophilic substitution of good leaving groups both in podand and heterocycle. When heterocycles interact with podands containing nucleofuges the reaction species can be either exocyclic nitrogen atom (Scheme 39)[97-102] or nucleophilic substituent in the heterocycle (Scheme 40).[103-106]



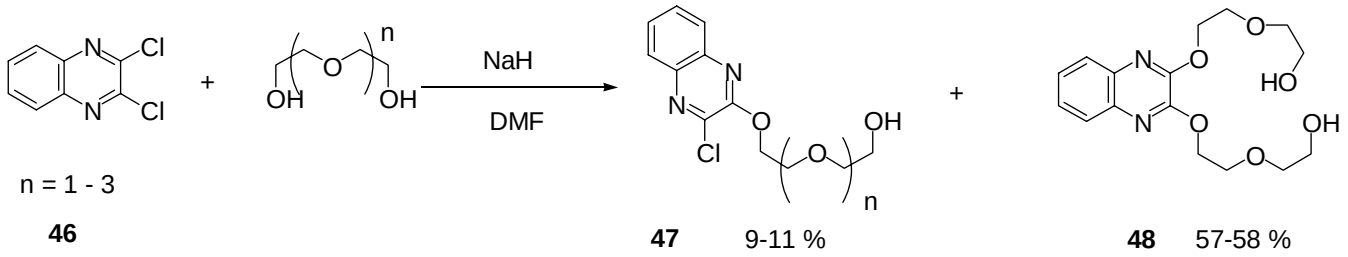
Scheme 39



Scheme 40

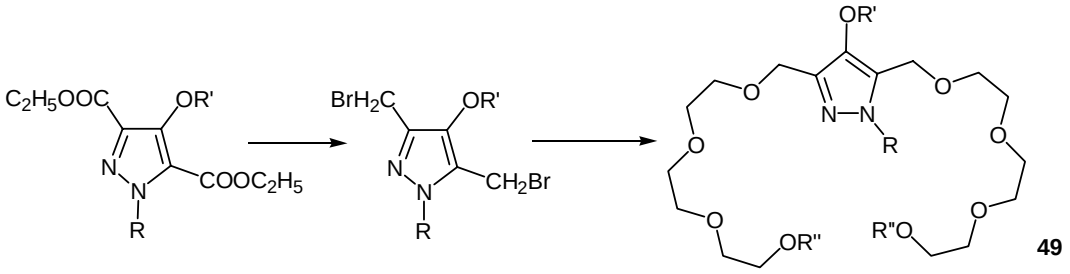
Depending on the number of good leaving groups in the parent compounds the products containing heterocyclic and polyether fragments in 1:1 or 1:2 ratio were obtained.

There are some literature examples of the synthesis of heteryl-containing podands by substitution of a good leaving group in heterocycle. Quinoxaline-containing podands (**47**) and (**48**) with moderate yields were prepared by the reaction of 2,3-dichloroquinoxaline (**46**) with sodium salt of polyether (Scheme 41).[107]



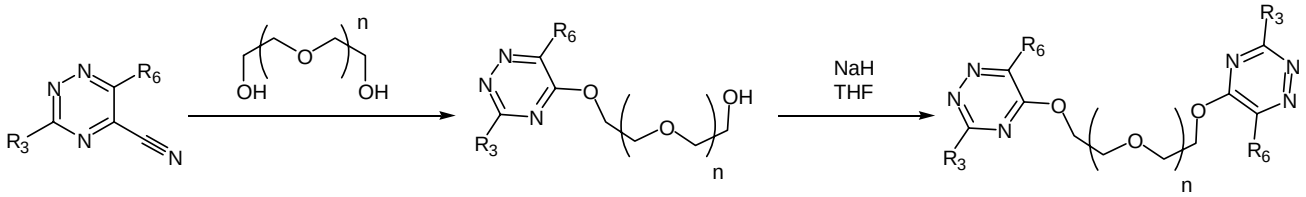
Scheme 41

The presence of two nucleophuges in the pyrazole ring promotes the appearance of two polyether moieties in the molecule (Scheme 42).[108] Obtained podand (**49**) extracts dopamine selectively.



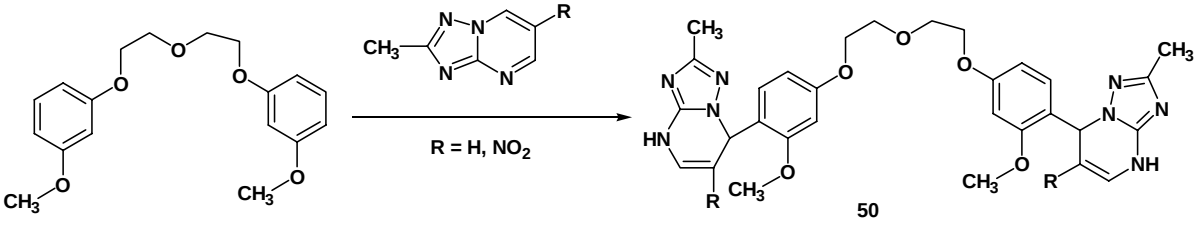
Scheme 42

The treatment of 5-cyano-1,2,4-triazines with polyethers leads to the substitution of cyanogroup (Scheme 43).[109]

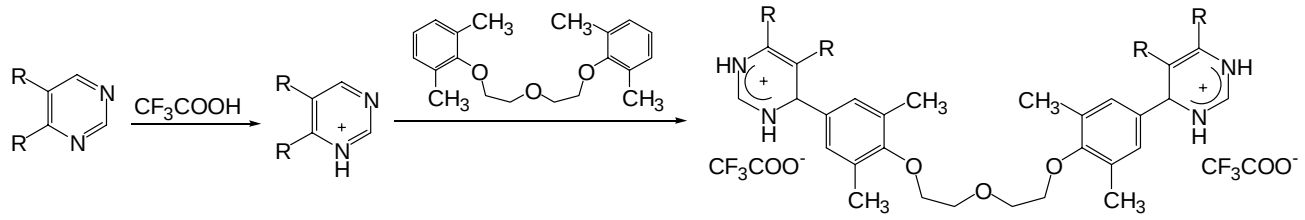


Scheme 43

Besides amino and hydroxy groups the terminal aromatic substituents of podands can play a role of a nucleophilic component. Ability of azines to addition of aromatic C-nucleophiles was used for the synthesis of heteryl-containing podands (**50**, **51**, **52**, **53**) (Schemes 44, 45, 46).[95, 110, 111]



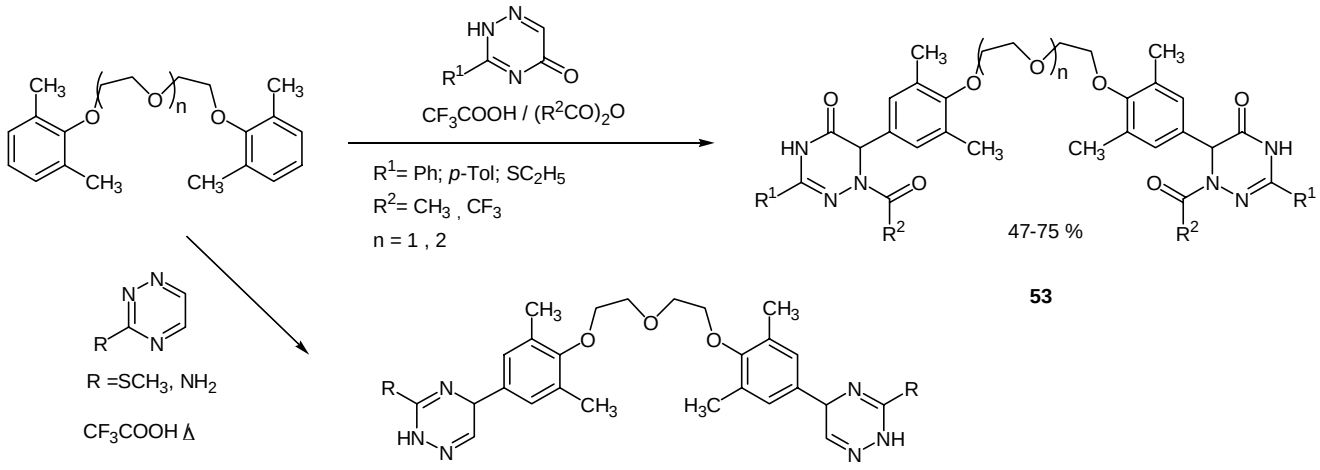
Scheme 44



51

R = H, benzo

Scheme 45

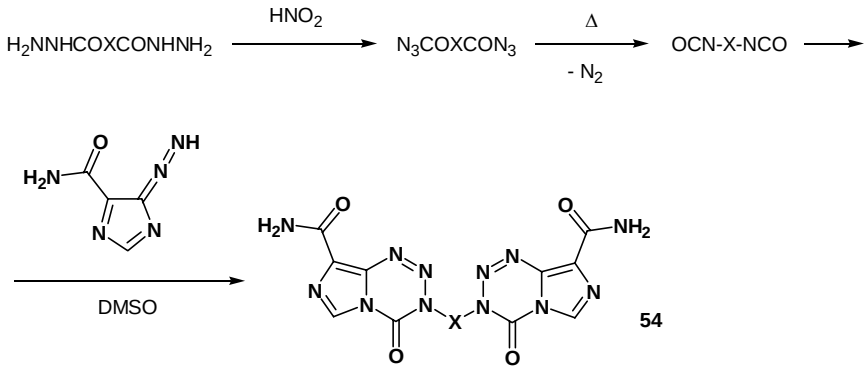


53

52

Scheme 46

Heterocyclization and rearrangements reactions caused by nucleophilic attack of polyethers or thiopolyethers are separative group of reactions. Scheme 47 shows building the fragments of antitumor agent "mitolozomide" on the base of polyether chain. This structural modification of the agent results in improving its membranotropic properties.[112]

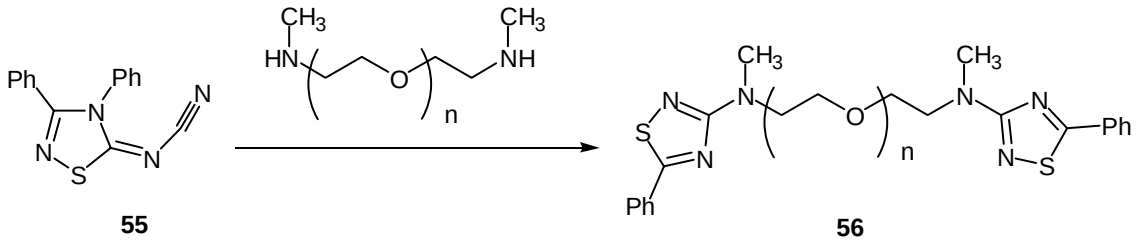


54

X = $(CH_2)n$, CH_2SCH_2, CH_2OCH_2, $CH_2O(CH_2)_2OCH_2$, $(CH_2)_2S(CH_2)_2$, $(CH_2)_2SCH_2S(CH_2)_2$, $(CH_2)_2SS(CH_2)_2$

Scheme 47

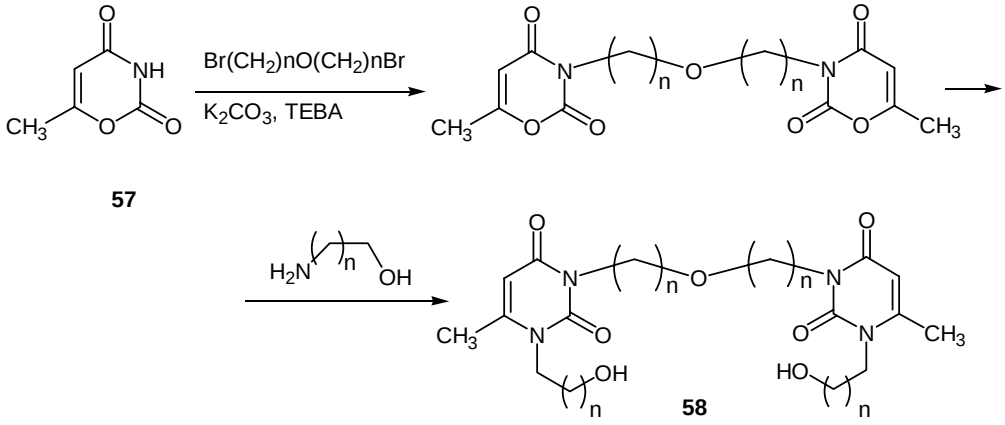
The appearance of podand chain in the heterocycle affects complexation ability of the molecule. The interaction of thiadiazole (**55**) with di(methylamino)polyether affords compound (**56**) which are able to extract metal cations in the order: $Cu^{2+}>>Pb^{2+}>K^{+}>Ni^{2+}>>Cd^{2+}$ (Scheme 48).[56]



55 **56**

Scheme 48

Pyrimidine-containing podands (**58**) forms by the reaction of 6-methyl-1,3-oxazine-2,4(3*H*)-dione (**57**) with dibromo polyether. The reaction is accompanied by oxazine ring opening and pyrimidine ring closing (Scheme 49).[113]

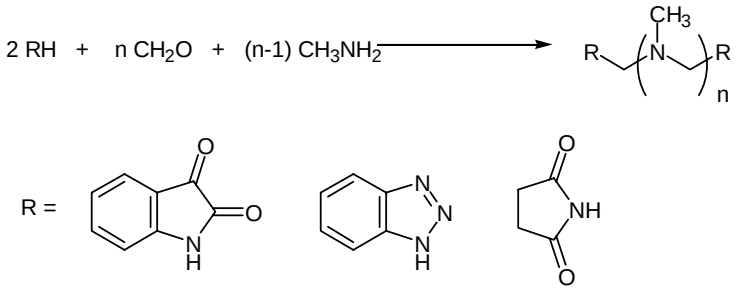


57 **58**

Scheme 49

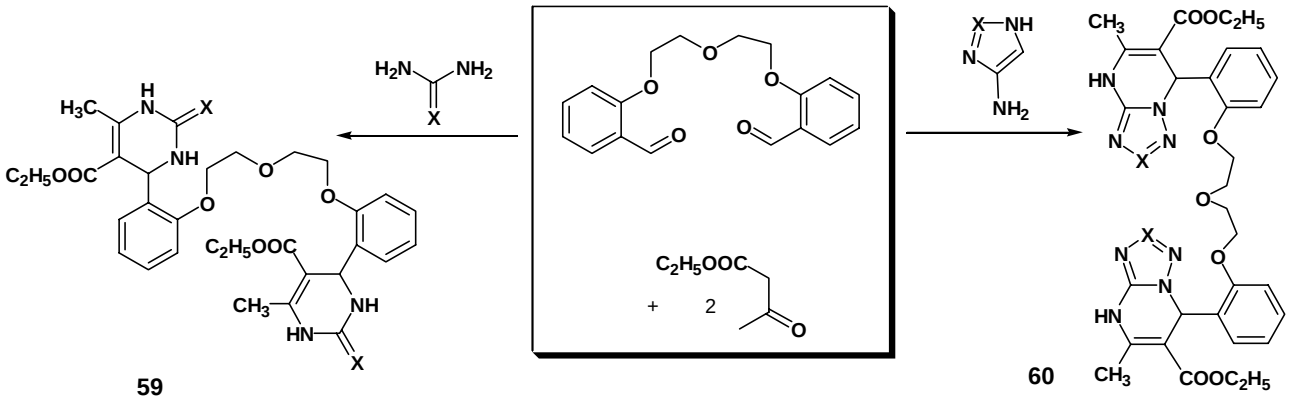
Podands having aromatic fragments are modified by the electrophilic substitution reactions, which increases functionalization degree of molecule.

Using multicomponent reactions makes it possible to obtain heteryl-containing podands in one stage. Thus Mannich reaction is a good route to the heterylpolyethylenepolyamines (Scheme 50).[114]



Scheme 50

Three-component Biginelly reaction allows preparation of dihydropyrimidine-containing podands (**59**) and (**60**) (Scheme 51).[115]



Scheme 51

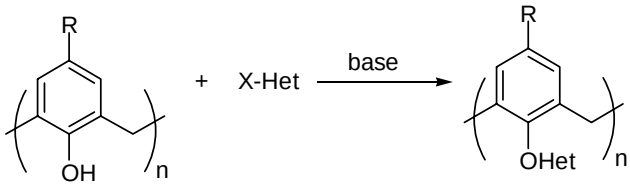
3. HETARYLATION OF CALIXARENES

Calixarenes, compounds of interesting shape, useful in supramolecular chemistry as a platform for creation of pre-organized receptors may be laterally substituted, functionalized at lower and upper rims, or bridging fragments of parent macrocycles. Of special interest is the introduction of heterocyclic moieties into calixarenes. In this case the additional complexation center for synthesis of selective ditopic receptors is appeared in the molecule. Functionalization by pyridyl and oligopyridyl fragments may be interesting to design ligands capable of selective binding and extraction of the Ag^{+},[116,117] Cs^{+},[118] Eu^{3+} and Tb^{3+},[119] Ru^{3+} and Rn^{+}.[120-123]

3.1. LOWER RIM MODIFICATION

There are two approaches for hetarylation of calixarene lower rim: nucleophilic substitution of good leaving groups in heterocycle ($S_N^{ipso}Ar$) and heterocyclization of open-chain substituents in the lower rim. The former method is more commonly used.

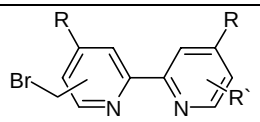
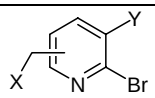
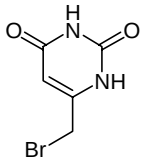
The reaction of bromo- and chloroheterocycles with calixarenes in the presence of a base in aprotonic solvent results in the products of partial or exhaustive hetarylation of hydroxy groups. The hetarylation degree depends on both substituents in the lower rim and the reaction conditions. (Scheme 52, Table 2) Such reaction affords the formation one or more conformers. Thus, it is very important to find reaction condition to prepare compounds with fix conformation.

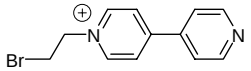
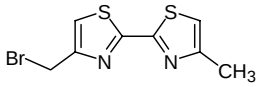
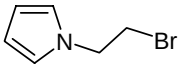


61 a-f **62 a-f**

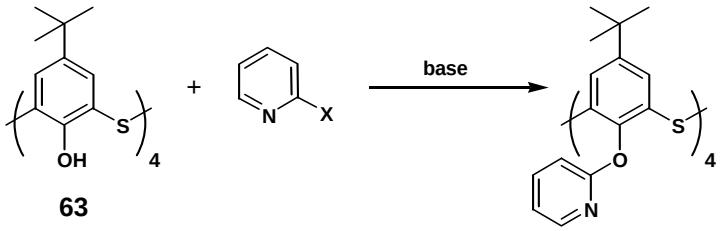
Scheme 52

Table 2. Reaction conditions and yields of **58 a-f**

No	R	n	HetX **61 a-f**	Reaction conditions	**62 a-f**	%	Ref.
a		4					
	t-C_4H_9		R=H, R'=CH_3	a) α,α'-isomer,			
				NaH/DMF	1,3- O-Het	50	124
				b) β,β'-isomer,			
				K_2CO_3/CH_3CN	1,3- O-Het	60	125
				NaH/DMF	1,2,3,4-O-Het	62	
	H		R=H, R'=H	α,α'-isomer,			
				NaH/DMF (1:4)	1,2,3,4-O-Het ***cone***	40	119
				K_2CO_3/CH_3CN(1:4)	1,2,3,4-O-Het ***1,3-alternate***	40	
				K_2CO_3/CH_3CN(1:2)	1,3-O-Het ***cone***	40	
	H		$R=COO^-$, R'=H	α,α'-isomer,			
				K_2CO_3/ CH_3CN, Δ	1,3-O-Het ***cone***	83	126
b							
	t-C_4H_9	3	X = Br, Y=H	α-isomer; NaH	1,2,3-O-Het	80	118
				K_2CO_3		95	
	t-C_4H_9	4	X=Br, Y=α-CH_2OH	α -isomer, NaH	1,3-O-Het	68	116
	t-C_4H_9	4	X=Cl, Y=H	a) α-isomer,			
				NaH/CH_3CN	1,2,3,4-O-Het	42	127
				Cs_2CO_3/DMF	1,3- + 1-O-Het	40	128
				b) γ-isomer,			117,
				NaH/CH_3CN	1,2,3,4-O-Het	32	129
c	C_6H_{13}	4			1,3-O-Het		130

No	R	n	HetX **61 a-f**	Reaction conditions	**62 a-f**	%	Ref.
d	*t*-C_4H_9	4					130
e	*t*-C_4H_9	4		BaO / $Ba(OH)_2$ / DMF	1-O-Het	35	132
f	*t*-C_4H_9	4		NaH / DMF	1,3-O-Het	40	131

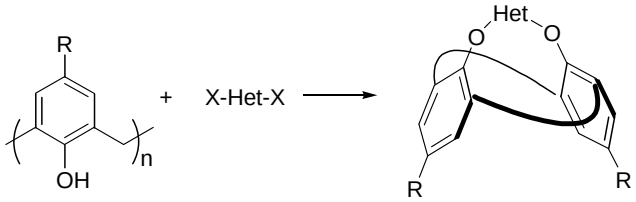
Hetarylation of lower rim of thiacalix[4]arene (**63**) is carried out in the similar way (Scheme 53).[133]



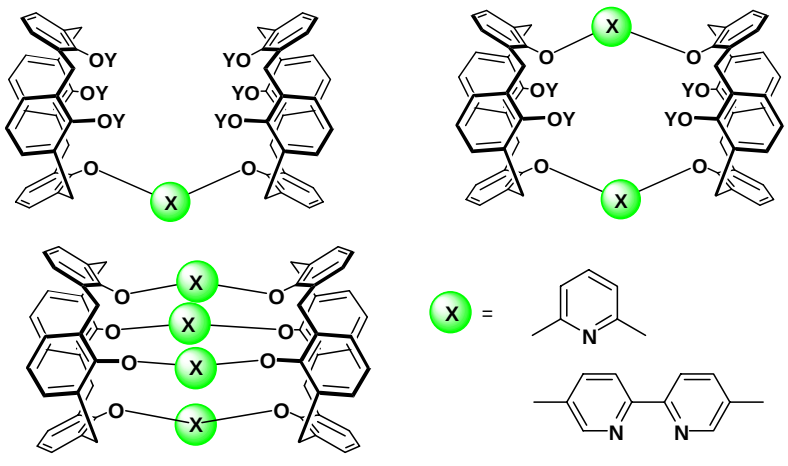
Scheme 53

The reactions of dihalogensubstituted azines with calixarenes afford the formation of bridging structures on the base of calix[4]arene[134] and calix[6]arene[129,135,136] or binding two calixarenes by heterocyclic fragments (Schemes 54, 55).[125,137-139]

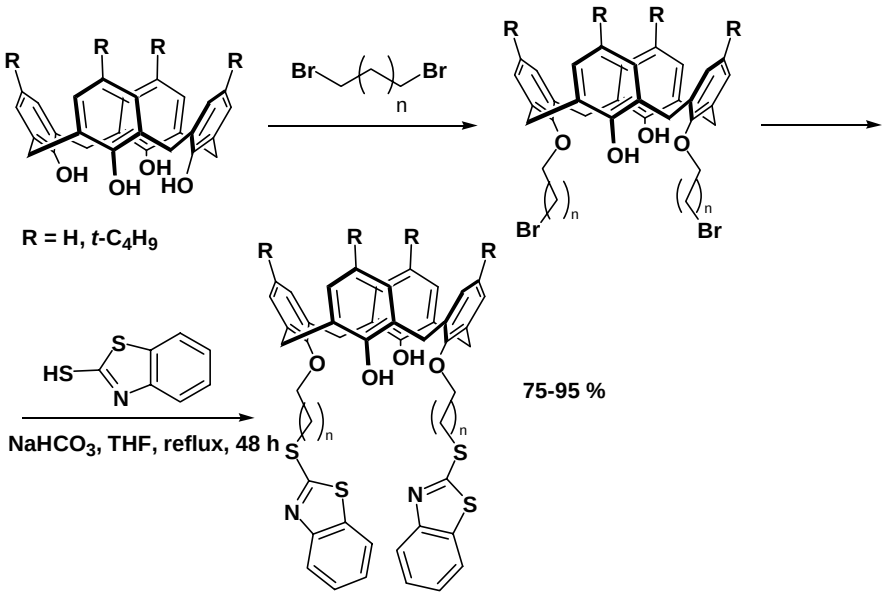
In the literature there is an example of heterylation of lower rim by the reaction of nucleophilic substitution of leaving group in calixarene (Scheme 56).[140]



Scheme 54

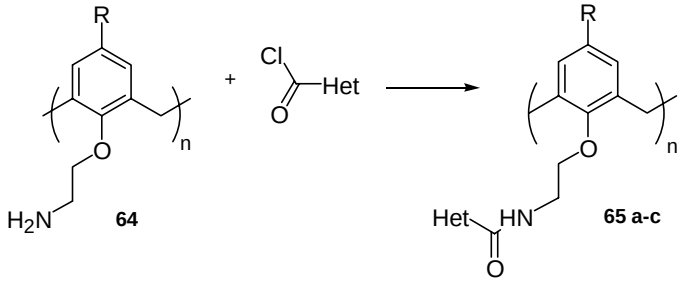


Scheme 55



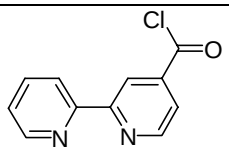
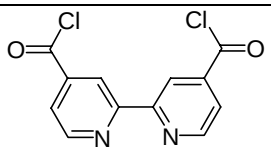
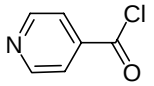
Scheme 56

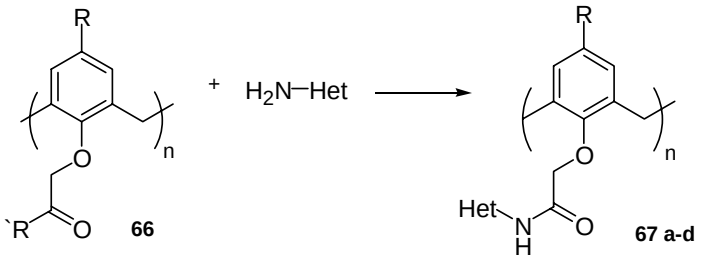
Another way for hetarylation of lower rim of calixarene die is aminolysis of acyl chlorides. The target products were created both by the interaction of aminocalixarene derivatives with chloroanhydrides of heterocycle-containing acyl chlorides (Scheme 57, Table 3) and by the reaction of aminosubstituted heterocycles with calixarenes having acyl chloride group (Scheme 58, Table 4).



Scheme 57

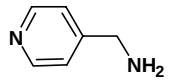
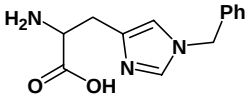
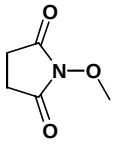
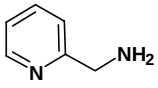
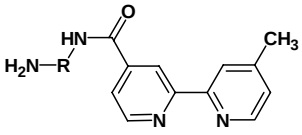
Table 3. Reaction conditions and yields of **65 a-c**

No	HetCOCl	R	n	%	Conditions	Ref.
a		H	6	55	$N(C_2H_5)_3$	141
b		*t*-C_4H_9	4	55	$N(C_2H_5)_3$, DMAP, CH_2Cl_2	120
c		C_6H_{13} *t*-C_4H_9	4 4	70 50	$N(C_2H_5)_3$ $N(C_2H_5)_3$	128, 142

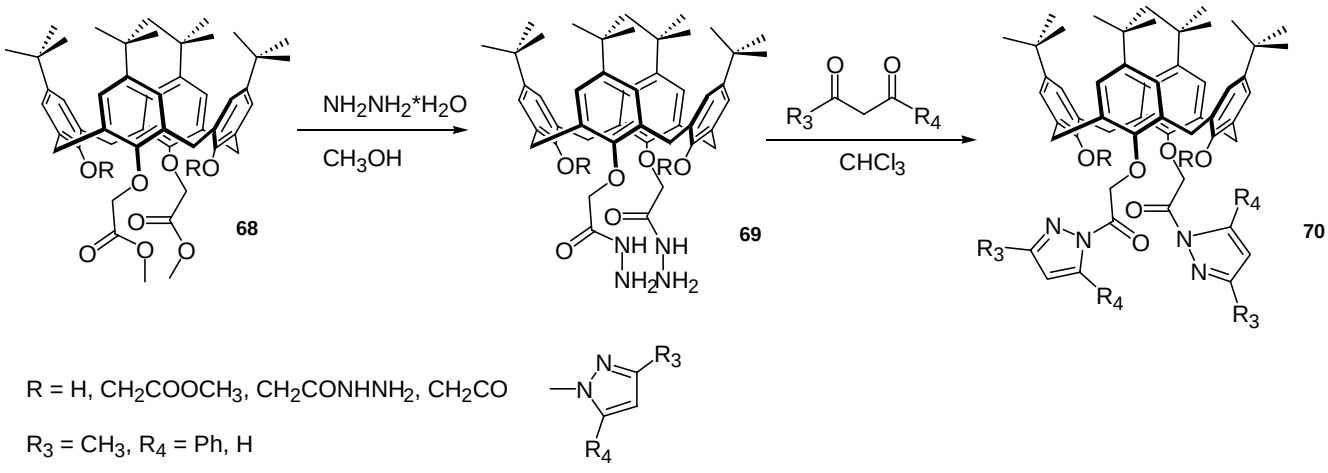


Scheme 58

Table 4. Reaction conditions and yields of **67 a-d**

No	$HetNH_2$	R`	R	n	%	Conditions	Ref.
a		Cl	*t*-C_4H_9	4	60	$N(C_2H_5)_3$, CH_2Cl_2	142
b			*t*-C_4H_9	4	45	HCl / $(i\text{-}C_3H_7)_2NC_2H_5$ CH_2Cl_2	143
c		OMe	*t*-C_4H_9	4	80	CH_3OH/CH_3Ph, reflux, 10 days	144
d		OEt	H	4	91	CH_2Cl_2, $N(C_2H_5)_3$, rt, 30 h	145

As a rule the third method of hetarylation of lower rim is a multistep procedure consisting in consecutive cyclization of open-chain structures. Hydrazine derivatives of 4-*tert*-butylcalix[4]arenes (**69**) were prepared by successive conversion of methoxycarbonylmethyl derivatives (**68**) into amides when treated by hydrazine hydrate.[146] The subsequent condensation of such compounds with different 1,3-diketones leads to the formation of pyrazole-containing calixarenes (**70**).[147] (Scheme 59)



R = H, CH_2COOCH_3, $CH_2CONHNH_2$, CH_2CO

$R_3 = CH_3$, R_4 = Ph, H

Scheme 59

3.2. UPPER RIM MODIFICATION

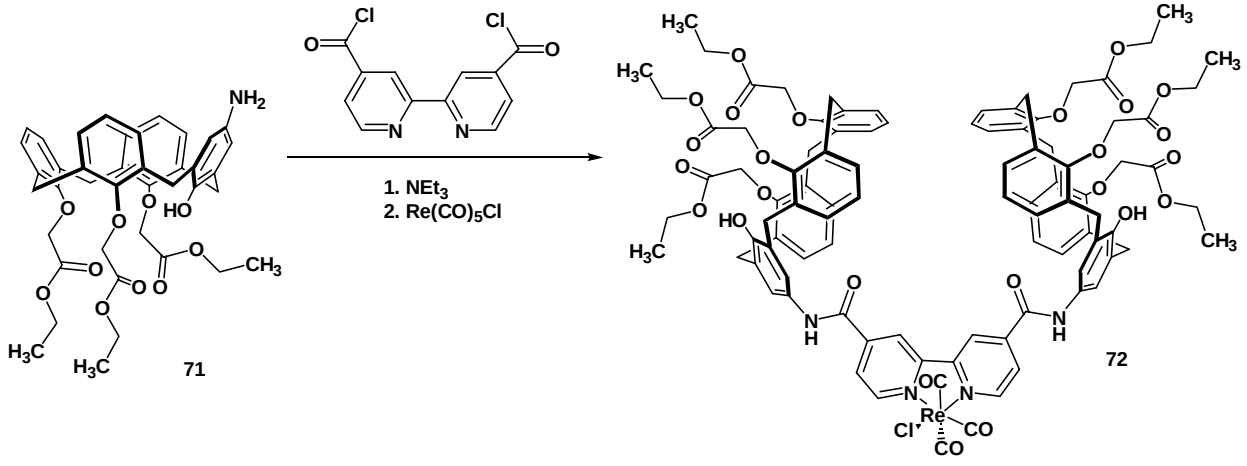
Compounds extracting I and II groups metal cations and bind anions and rare-earth metal cations due to complexation centers divided in the space are formed by modification of upper rim of calixarene. Hetarylation of upper rim is topical for the design of a new generation of lowtoxical biologically active compounds. Namely calixarene platform fixes the sterical location of heterocyclic receptors and promotes more selective binding the active centers of biological target.[4]

In most cases modification of upper rim of calixarene die is a multistage process requiring preliminary functionalization of aromatic rings.

The studies concerned with this problem divide into three groups:

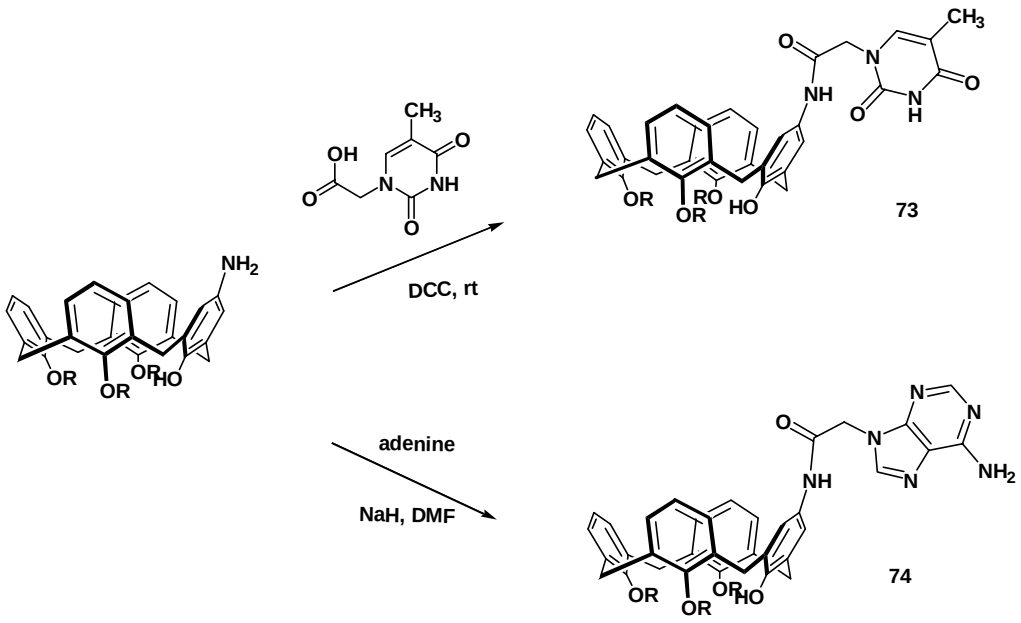
- Synthesis of hetaryl-containing calixarenes by modification of amino derivatives of calixarenes obtained by the conversion of compounds available in electrophilic substitution reaction (nitration, halogenation, sulphurizing)
- Hetarylation of calixarenes having formyl-group at the upper rim
- Direct coupling of unsubstituted calixarenes and heterocycles

Introduction of amino group into aromatic ring is well-known synthetic route, so most of works presented in the literature are devoted to this method. As a rule amino derivatives of calixarenes are formed by nitration of aromatic ring followed by reduction of nitro-group.[120, 121, 148, 149] Amino-substituted calixarenes readily react with hetaryl-containing carboxylic acids.[120,149] The interaction of aminocalixarenes (**71**) with 2,2'-dipyridyl derivatives acyl chlorides results in product (**72**) in which two calixarenes are bound by heterocyclic fragment (Scheme 60).[121,148]



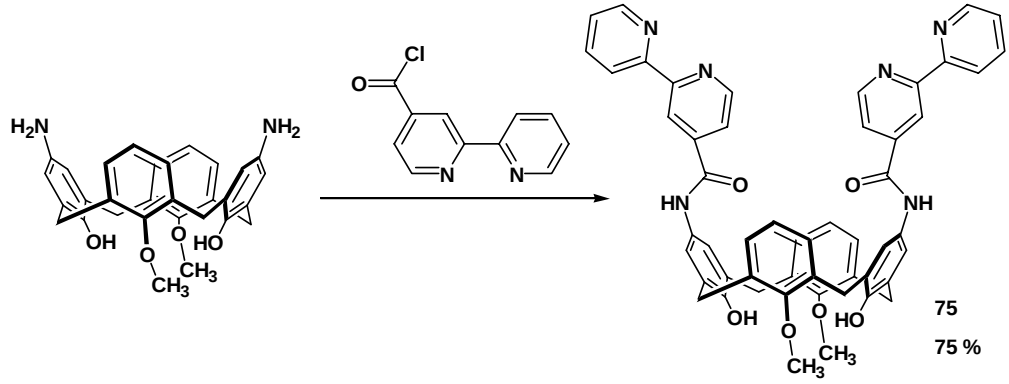
Scheme 60

Calixarenes (**73**) and (**74**) having one heterocyclic moiety are prepared by the reaction with pyrimidines:[148]

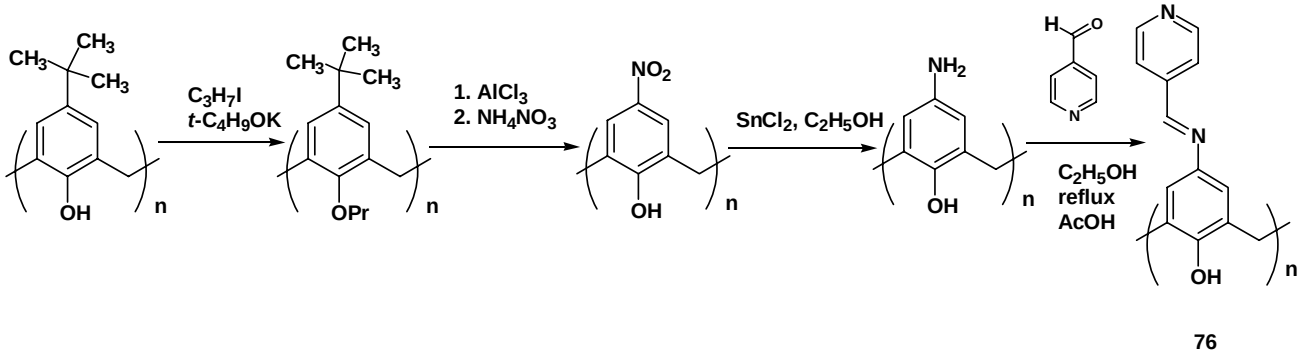


Scheme 61

Varying the number of functional substituents at the upper rim allows to obtaining products (**75**) and (**76**) with two and more heterocyclic fragments (Scheme 62, Scheme 63).[123]

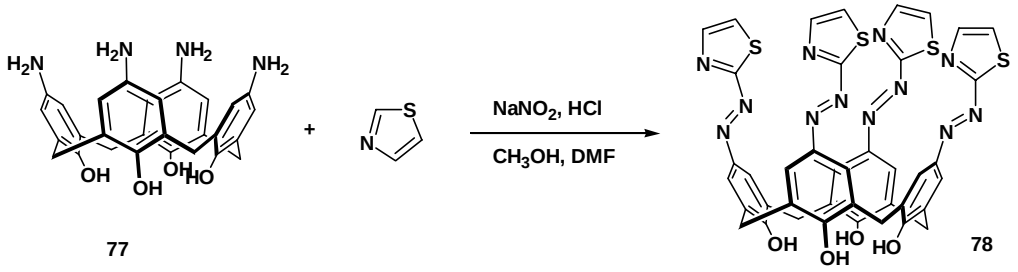


Scheme 62



Scheme 63

Due to easy diazotizing of amino-groups it is possible to carry out azo-coupling of aminocalixarene (**77**) with thiazole.[150]

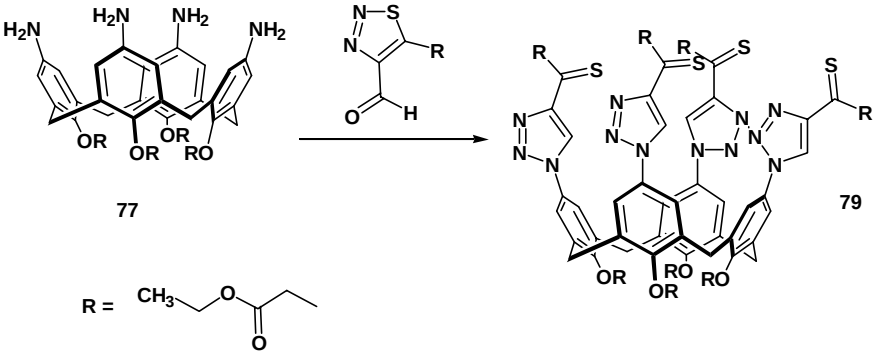


Scheme 64

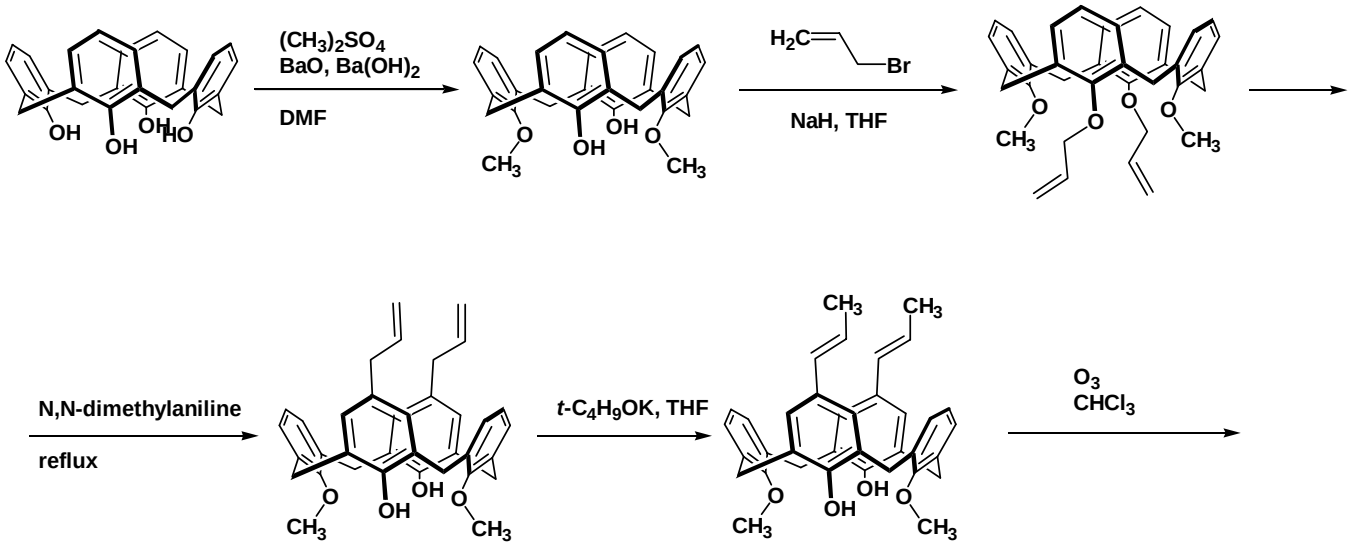
Calixarene directly bound with heterocyclic substituent is obtained due to susceptibility of five-member thiazoles to rearrangement by the action of N-nucleophiles. For example, the reaction of aminocalixarene (**77**) with 1,2,3-thiadiazolyl-4-carbaldehyde results in the formation of imines followed by easy Cornfort rearrangement into 1,2,3-triazole-containing calixarene (**79**) (Scheme 65).[151]

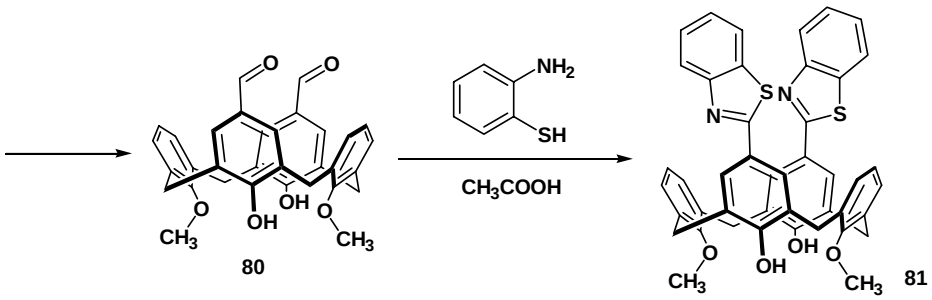
As mentioned above, the use of formyl function in calixarene also promote to build heterocyclic substituents at the upper rim.

Thus, condensation of 1,3-diformylcalixarene (**80**) with 2-aminothiophenol leads to the calixarene modified by benzothiazole (**81**) (Scheme 66).[152]



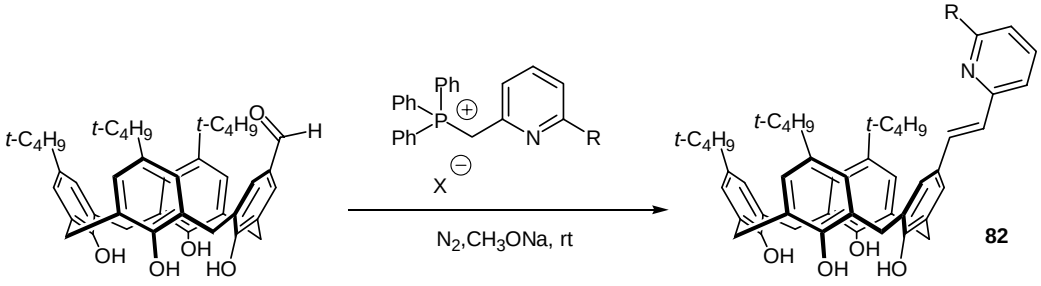
Scheme 65





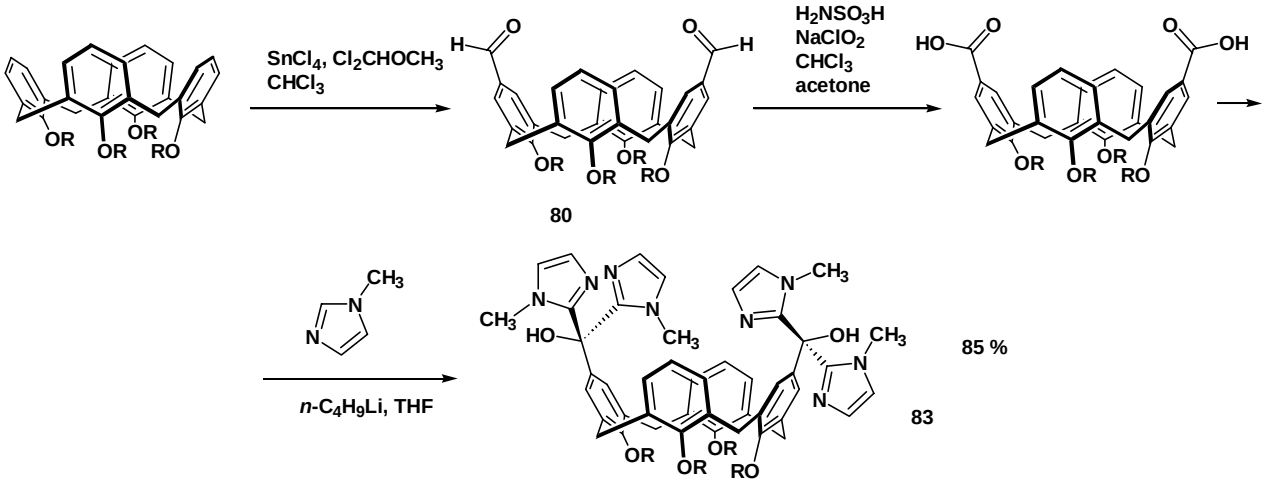
Scheme 66

Wittig reaction is the successful method for preparation of pyridine-containing calixarenes (**82**).[153]

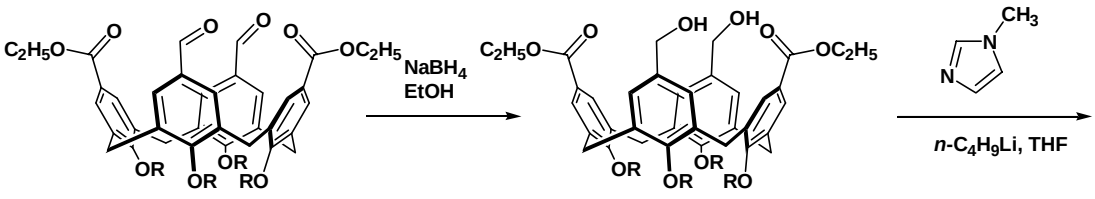


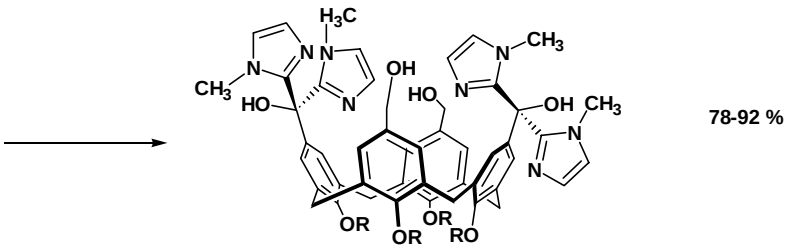
Scheme 67

Compounds (**83**) and (**84**) were obtained by the reaction of calixarenes (**80**) having formyl group with 2-methylimidazole (Schemes 68, 69). Their complexes with Zn^{2+} and Cu^{2+} cations can be considered as synthetic models of enzymes.[154,155]



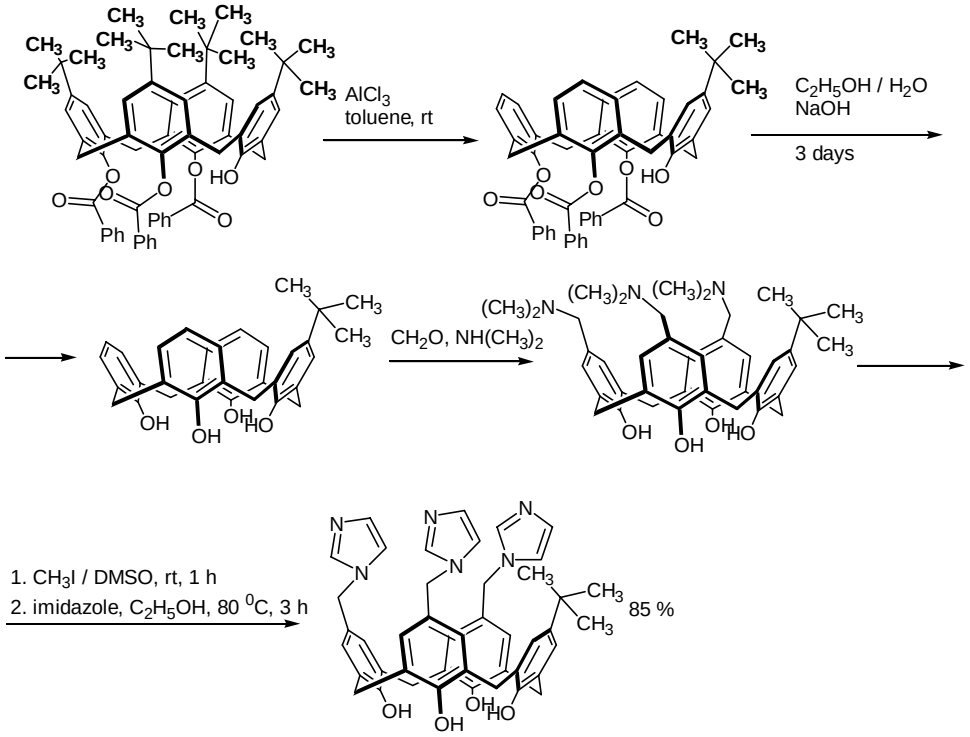
Scheme 68





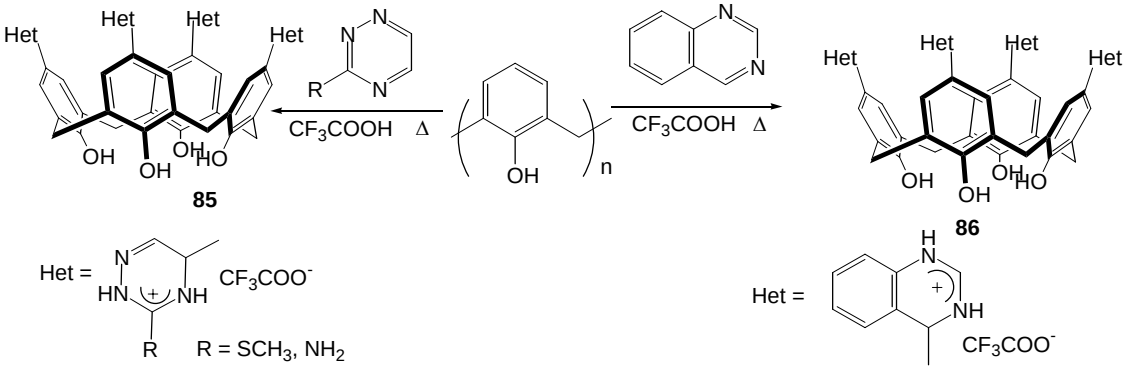
Scheme 69

Mannich reaction is the efficient route to hetarylation of upper rim of calixarene die (Scheme 70).[156,157]



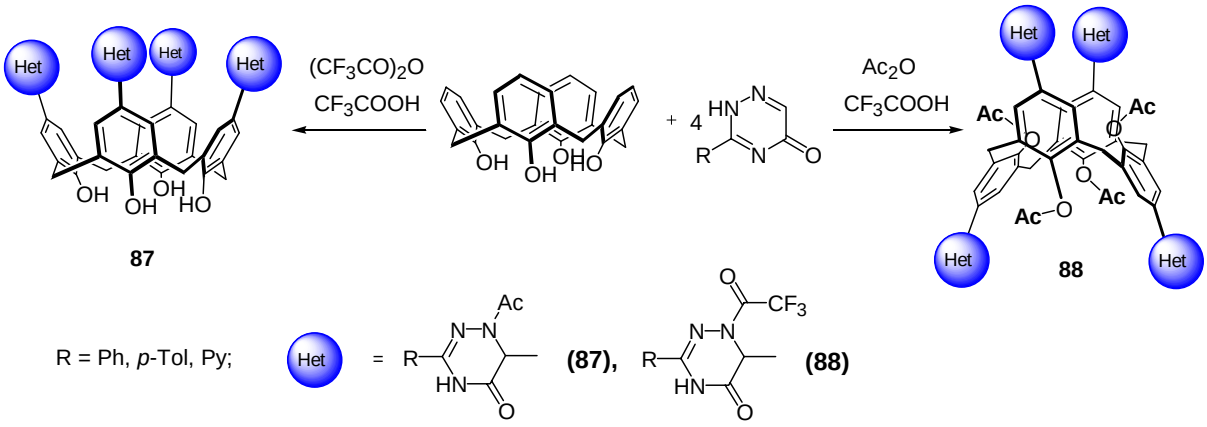
Scheme 70

Unsubstituted calixarenes exhibit nucleophilic properties not only in Mannich reaction but also in the interaction with π-deficient heterocycles. Using methodology of direct C-C coupling of azaheterocycles with aromatic C-nucleophiles[92] a products of exhaustive hetarylation of upper rim of calixarene die by the reaction with 1,2,4-traizines (**85**) and quinazoline (**86**) were obtained (Scheme 71).[95]



Scheme 71

It has been found that the reaction of calixarenes with 3-substituted 1,2,4-triazin-5-ones results in the products (**87)** and (**88)** in the fixed conformation (Scheme 72).[95]



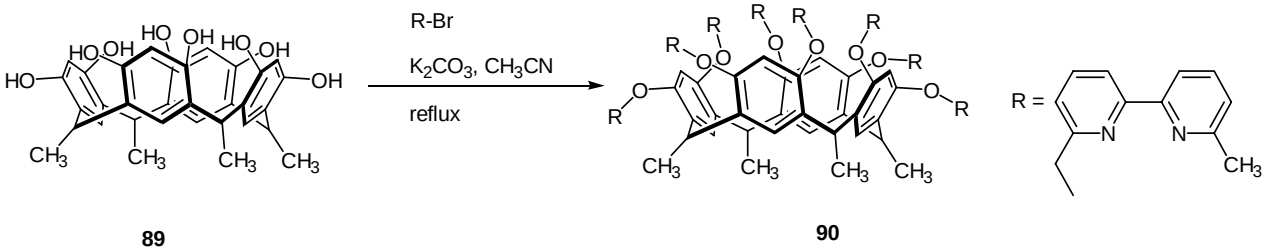
Scheme 72

Addition of organic anhydrides into reaction mixture is necessary to activate of 1,2,4-traizinones and form stable products. If the reaction is carried out of the reaction in the presence of acetic anhydride the acylation of lower rim of calixarene promotes conformerization into 1,3-alternate.[158] The same effect has been observed in the presence of trifluoroacetic anhydride. However in the latter case the dezacylation of hydroxy-groups proceeds and product in cone conformation was isolated.

4. SYNTHESIS OF RESORCINARENES MODIFIED BY AZAHETEROCYCLES

Resorcinearenes and cavitands are of special interest in the diversity of molecular receptors. To our knowledge calixresorcinarenes are one of ligands having permanent conformation (cone) and fixed size of the cavity. Most of different complexation centers allows binding a great number of cations and anions. The presence of several reaction centers in the molecule allows its modification both at upper and middle rim.

Contrary to calixarene modification there are only a few examples describing the functionalization of resorcinearenes and cavitands by heterocyclic fragments. Such resorcinarene derivatives can be easily modified at hydroxyl groups, which results in the increase of comlexation cavity volume. So, the main method for functionalization of resorcinarenes is the alkylation reaction, in which hydroxy-groups act as a nucleophile. The interaction of resorcinarene (**89**) with eight equivalents of 6-bromomethyl-6'-methyl-2,2'-dipyridyl gives the product (**90**) of exhaust O-alkylation of upper rim of resorcinarene die (Scheme 73).[159]



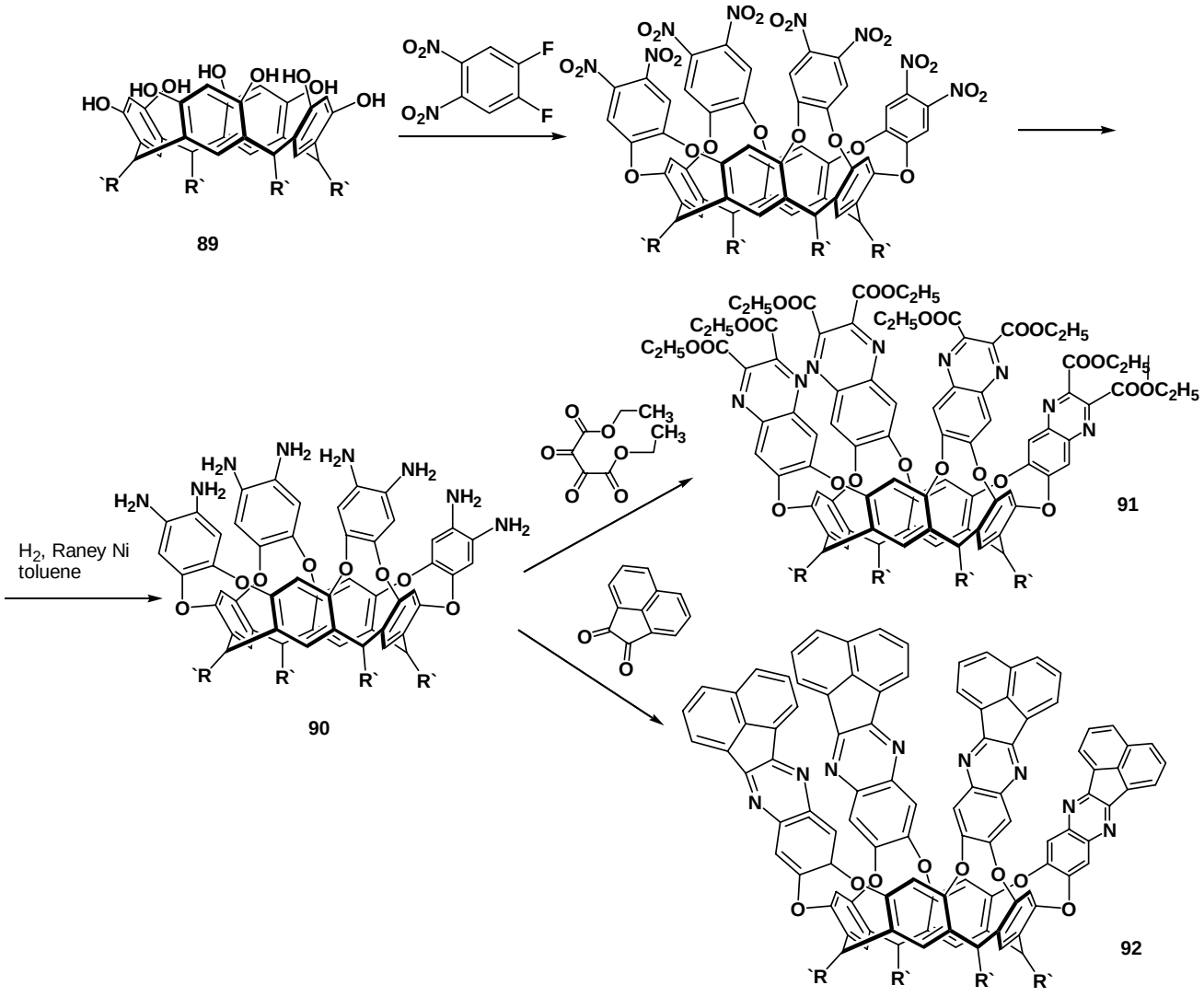
Scheme 73

Halide atoms in 1,2-dinitro-4,5-difluorobenzene can by easily displaced by hydroxy-groups of **89**.

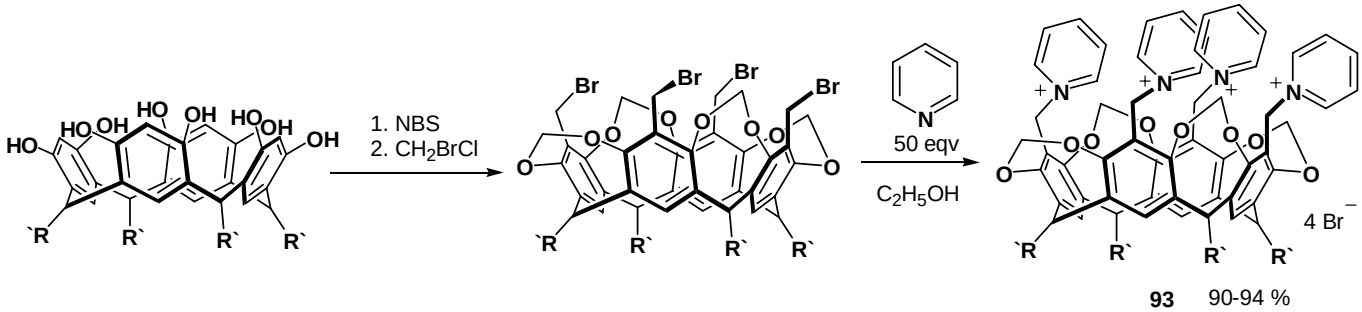
Treatment of **90** with 1,2-diketones results in the appearance of heterocyclic units in the molecule to give compounds (**91**) and (**92**) (Scheme 74).[160,161]

Similar transformations can be used for grafting calixarenes to porphyrines.[162]

Two examples of upper rim hetarylation of aromatic rings of resorcinarene are known. Treatment of bromomethyl derivative of resorcinarene by pyridine affords the quaternization and formation of charged structure (**93**) (Scheme 75).[163]

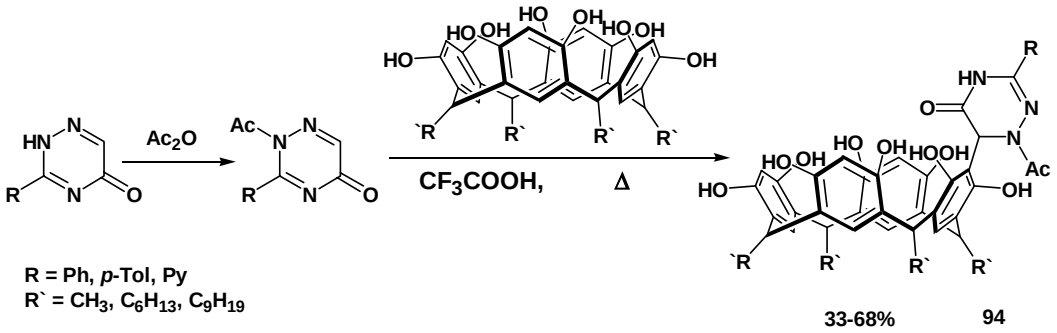


Scheme 74



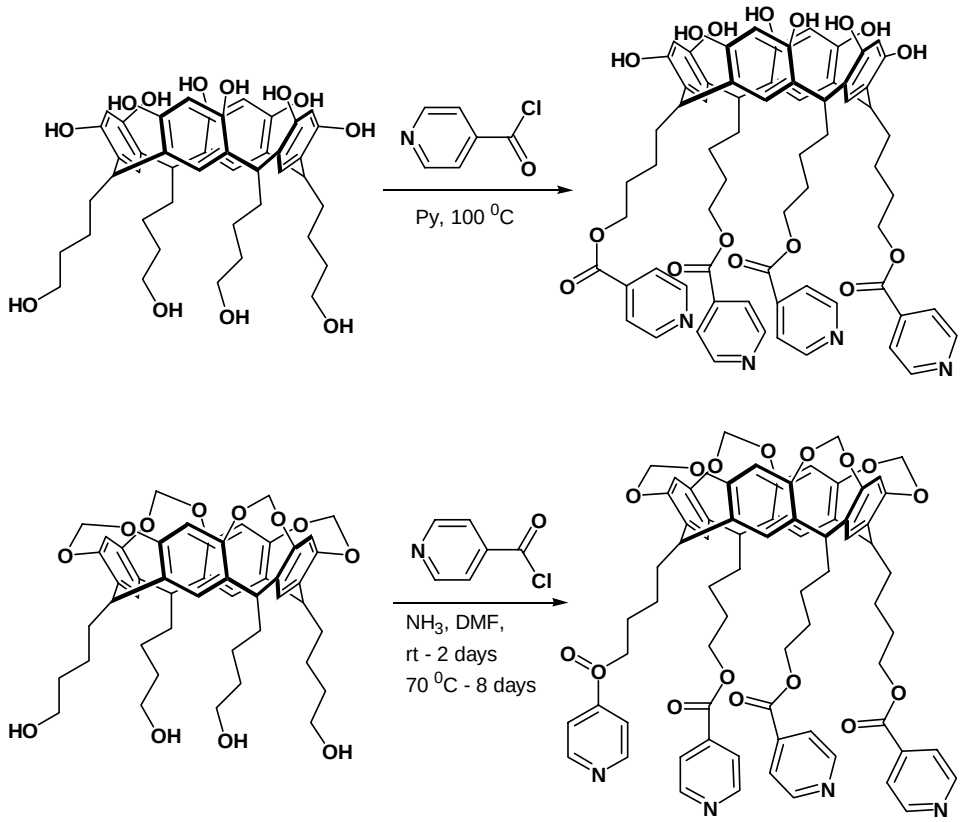
Scheme 75

Direct C-C coupling resorcinarenes with heterocycles has been carried out using the above mentioned A_N-methodology.[93,94] One-stage coupling of resorcinarene with 1,2,4-triazin-5-ones, based on the reaction of direct nucleophilic addition to unsubstituted carbon atom of azine, leads to formation of product (**94**) having one triazinone ring (Scheme 76).[164]



Scheme 76

There are a number of examples of hetarylation of resorcinarene bridging substituents. The presence of bridging fragment with terminal double bond into resorcinarene or cavitand molecule allows introducting nucleophilic by acylation hydroxy-group. In such compounds the first to react are hydroxy-groups of bridging substituents (Scheme 77).[163]



Scheme 77

The introduction of heterocyclic fragments into the resorcinarenes and cavitands gives a good possibility to increase the water solubility of these compounds.[163] The appearance of novel complexation centers in the molecule makes for selective extraction of Co^{2+} [156], Ni^{2+} and Pd^{2+}.[163]

CONCLUSION

Synthesis of macrocycles with heterocyclic substituents forms the basis of creating compounds having unique properties. The main synthetic approaches to these compounds are the reactions of nucleophilic substitution of halogen at sp^3- and sp^2-carbon atoms both in macrocycles and heterocyclic compounds, and consecutive building a heterocycle on the macrocyclic die. The limitation of the described methods is the need of preliminary modification of subtrates and that such reactions are multistage processes. At present the direct building of C-C bond between heterocycle and macrocycle is not common. It is described in the papers dealing with homolytical hetarylation of crown ethers (Minisci procedure), and direct coupling of unsubstituted macrocyclic system with different azine derivatives using A_N и S_N^H-methodology.

REFERENCES

1. J. - M. Lehn, 'Supramolecular Chemistry'; VCH', Weinheim, New York, Basel, Cambridge, Tokyo, 1995.
2. W. A. Smit, A. F. Bochkov, and R. Caple, 'Organic Synthesis', 'The Royal Society of Chemistry', 1998.
3. J. H. Hartley, T. D. James, and Ch. J. Ward, *J. Chem. Soc. Perkin Trans. 1*, 2000, 3155.
4. F. C. J. M. van Veggel, W. Verboom, and D. N. Reinhoudt *Chem. Rev*., 1994, **94**, 279.
5. R. M. Izatt, K. Pawlak, J. S. Bradshaw, and R. L. Bruening, *Chem. Rev.,* 1995, **95**, 2529.
6. C. J. Pedersen, *J. Am. Chem. Soc.,* 1967, **89**, 7017.
7. H. Tsukube, J. - I. Uenishi, N. Kojima, and O. Yonemitsu, *Tetrahedron Lett.,*1995, **36**, 2257.
8. R. M. Izatt, D. V. Dearden, Ph. R. Brown, J. S. Bradshaw, J. D. Lamb, and J. J. Christensen, *J. Am. Chem. Soc.*, 1983, **105**, 1785.
9. H. Tsukube, H. Minatogawa, M. Munakata, M. Toda, and K. Matsumoto, J. Org. Chem., 1992, **57**, 542.
10. H. Tsukube, J. Uenishi, H. Higaki, K. Kikkawa, T. Tanaka, Sh. Wakabayashi, and S. Oae, *J. Org. Chem.,* 1993, **58**, 4389.
11. Y. Habata, Y. Yamashita, and S. Akaboru, *J. Chem. Soc. Dalton Trans.,* 2001, 966.
12. B. Linton, and A. D. Hamilton, *Chem. Rev.,*1997, **97**, 1669.
13. L. Prodi, M. Montalti, N. Zaccheroni, J. S. Brandshaw, R. M. Izatt, and P. B. Savage, *Tetrahedron Lett.,* 2001, **42**, 2941.
14. G. Hennrich, H. Sonnenschein, and U. Resch-Genger, *Eur. J. Org. Chem.*, 2000, 539.
15. P. Huszthy, E. Samu, B. Vermes, G. Mezey-Vándor, M. Nogradi, J. S. Bradshaw, and R. M. Izatt, *Tetrahedron,*1999, **55**, 1491.
16. E. Samu, P. Huszthy, G. Horváth, Á. Szöllösy, and A. Neszmélyi, *Tetrahedron Asymmetry*, 1999,

3615.
17. K. L. Bushell, M. Couchman, J. C. Jeffery, L. H. Rees, and M. D. Ward, *J. Chem. Soc., Dalton Trans.*, 1998, 3397.
18. S. Sariguel and O. Bekaloglu, *Chem. Ber*, 1989, **122**, 291.
19. P. D. Beer, O. Kocian, R. J. Mortimer, and Ch. Ridgway, *J. Chem. Soc., Chem. Commun.*, 1991, 1460.
20. M. Schimittel, H. Ammon, and C. Wohrle, *Chem. Ber.,* 1995, **128**, 845.
21. P. D. Beer, O. Kocian, R. J. Mortimer, and Ch. Ridgway, *J. Chem. Soc., Dalton Trans.*, 1993, 2629.
22. M. Hiraoka. Crown compounds. Their Characteristics and Applications. Amsterdam, Oxford, NY, Elsivier Scientific, 1982.
23. A. Kleeman, J. Engel, and B. Kutscher, 'Pharmaceutical Substances: Synthesis, Patents, Application', 'Thieme Medical Pub', 2001.
24. K. French and F. Vögtle, *Tetrahedron Lett.*, 1977, 2573.
25. M. Timko, R. C. Helgeson, N. Newcomb, G. W. Gokel, and D. J. Cram, *J. Am. Chem. Soc.*, 1974, **96**, 7097.
26. F. Wudl and F. Gaeta, *J. Chem. Soc., Chem. Commun.*, 1972, 107.
27. T. Wang, J. S. Bradshaw, and R. M. Izatt, *Gazz. Chim. Ital.*, 1996, **126**, 159.
28. A. V. Bordunov, P. C. Hellier, J. S. Bradshaw, N. K. Dalley, X. Kou, X. X. Zhang, and R. M. Izatt, *J. Org. Chem.*, 1995, **60**, 6097.
29. A. Bencini, C. Giorgi, V. Fusi, A. Masotti, and P. Paoletti, *J. Org. Chem.*, 2000, **65**, 7686.
30. A. Huszthy, M. Oue, J. S. Bradshaw, Ch. Y. Zhu, T. Wang, N. K. Dalley, J. C. Curtis, and R. M. Izatt, *J. Org. Chem.,* 1992, **57**, 5383.
31. L. I. Ukhova, A. A. Zenyuk, and A. N. Sergeeva, *Chem. Heterocycl. Compd. (Engl. Transl.)* 1984, **20**, 1049.
32. Z. Pourghobadi, F. Seyye Majidi, M. Daghighi-Asli, F. Parsa, A. Moghimi, M.R. Ganjiali, H. Aghabojorg, and M. Shamaipur, *Polish J. Chem.,* 2000, **74**, 837.
33. K. Suwiñska, *Acta Cryst. Section C*, 1995, 2232.
34. M. Peters, M. L. Hallensleben, and M. van Hooren, *J. Mater. Chem.,* 1999, 1465.
35. H. - S. Kim, I. - Ch. Kwon, and J. - H. Choi, *J. Heterocycl. Chem.,* 1999, **36**, 1285.
36. M. I. Rodríguez-Franco, P. San Lorenzo, A. Martinez, and P. Navarro, *Tetrahedron*, 1999, **55**, 2763.
37. P. Huszthy, Z. Köntös, B. Vermes, and Ā. Printēr, *Tetrahedron,* 2001, **57**, 4967.
38. A. Vichet, A. - M. Patellis, J.- P. Galy, A.- M. Galy, J. Barbe, and J. Elguero, *J. Org. Chem.,* 1994, **59**, 5156.
39. H. Zhao and W. Hua, *J. Org. Chem.,* 2000, **65**, 2933.
40. Yi Li, L. Echegoyen, M.V. Martinez-Diaz, J. D. Mendoza, and T. Torres, *J. Org. Chem.,* 1991, **56**, 4193.
41. R. B. Davidson, N. K. Dalley, B. A. Jones, J. S. Bradshaw, J. J. Christensen, and J. James, *J. Org. Chem.,* 1984, **49**, 353.

42. Yi Li and L. Echegoyen, *J. Org. Chem.*, 1994, **59**, 6539.
43. A. Roigk and H. J. Schneider, *Eur. J. Org. Chem.,* 2001, 205.
44. N. Su, J. S. Bradshaw, X. X. Zhang, P. B. Savage, K. E. Krokowiak, and R. M. Izatt, *J. Heterocycl. Chem,* 1999, **36**, 771.
45. A. R. Katritzky, S. A. Belyakov, and A. E. Sorochinsky, *J. Org. Chem.,* 1996, **61**, 7585.
46. O. Murillo, E. Abel, G. E. M. Maguire, and G. M. Gokel, *Chem. Commun.,* 1996, 2147.
47. Sh. Yamazaki, M. Hanada, Yui. Yanasei, Ch. Fukumori, K. Ogura, T. Saeki, and Sh. Umetani, *J. Chem. Soc., Perkin Trans.1,* 1999, 693.
48. H. Tsukube, *J. Syn. Org. Chem. Jpn.*, 1993, **51**, 851.
49. G. Xue, J. S. Bradshaw, N. K. Dalley, P. B. Savage, K. E. Krakowiak, R. M. Izatt, L. Prodi, M. Montalti, and N. Zaccheroni, *Tetrahedron*, 2001, **57**, 7623.
50. N. Su, J. S. Bradshaw, X. X. Zhang, H. Song, P. B. Savage, G. Xue, K. E. Krakowiak, and R. M. Izatt, *J. Org. Chem.,* 1999, **64**, 8855.
51. G. V. Fedorova, E. I. Ivanov, A. V. Lobach, O. N. Leus, and N. G. Lukyanenko, *Russ. J. Org. Chem.*, 1994, **30**, 464.
52. E. I. Ivanov, G. V. Fedorova, O. G. Yasinskaya, A. N. Musienko, V. V. Ivanova, A. V. Mazepa, and B. V. Kunshenko, *Russ. Chem.-Pharm. J.,* 1992, 66.
53. S. Alihodzic, M. Zinic, B. Klaic, R. Kiralj, B. Kojicprodic, M. Herceg, and Z. Cimerman, *Tetrahedron Lett.*, 1993, **34**, 8345.
54. B. Whittle, S.R. Batten, J. C. Jeffery, L. H. Rees, and M. D. Ward, *J. Chem. Soc., Dalton Trans.,*1996, 4249.
55. Yam V. Wing-Wang and V. Wing-Man Lee, *J. Chem. Soc., Dalton Trans.,* 1997, 3005.
56. L. Pirondini, D. Bonifazi, E. Menozzi, E. Wegelius, K. Rissanes, Ch. Massera, and E. Dalcanale, *Eur. J. Org. Chem.,* 2001, 2311.
57. M. Tanaka, K. Kamada, H. Ando, T. Kitagaki, Ya. Shibutani, and K. Kimura, *J. Org. Chem.,* 2000, **65**, 4342.
58. O. A. Fedorova, S. P. Gromov, Yu. V. Pershina, S. S. Sergeev, Yu. P. Strokach, and V. A. Barachevsky, *J. Chem. Soc., Perkin Trans.2,* 2000, 563.
59. O. A. Fedorova, S. P. Gromov, and M. V. Alfimov, *Russ. Chem. Bull.*, 2001, **50**, 1970.
60. I. K. Lednev, O. A. Fyudorova, S. P. Gromov, M. V. Alfimov, J. N. Moore, and R. E. Hester, *Spectrochim. Acta, Part A,* 1993, **49**, 1055.
61. S. P. Gromov, E. N. Ushakov, O. A. Fedorova, V. A. Soldatenkova, and M. V. Alfimov, *Russ. Chem. Pharm. Bull,*. 1997, **46**, 1143.
62. O. A. Fedorova, E. N. Andryukhina, A. V. Lindeman, S. S. Basok, G. Yu. Bogatchenko, and S. P.Gromov, *Russ. Chem. Bull.*, 2002, 302.
63. S. S. Zlotskii, L. G. Kulak, and D. L. Rakhmankulov, *Bashk. Khim. Zhurn. (Rus),* 1996, **3**, 38.
64. A. Katoh, S. Ueda, J. Ohkanda, M. Hirota, H. Komine, and K. Mituhashi, *Heterocycles,* 1992, **34**, 1965.

65. K. Mitsuhashi, Y. Nagae, and T. Suzuki, *J. Heterocycl. Chem.,* 1986, **23**, 1741.
66. S. Iwata and K. Tanaka, *J. Chem. Soc., Chem. Commun.,* 1995, 1491.
67. Yu. B. Zelechonok, V. V.Zorin, S. S. Zlotskii, and D. L. Rakhmankulov, *Chem. Hetrocycl. Compd.* (Engl. Transl.), 1985, **21**, 1056.
68. Yu. B. Zelechonok, L. P. Ivanova, V. V. Zorin, S. A. Kotlyar, S. S. Zlotskii, and D. L. Rakhmankulov, *Chem. Heterocycl. Compd.* (Engl. Transl.), 1988, **24**, 64.
69. L. P. Ivanova, Yu. B. Zelechonok, V. V. Zorin, S. S. Zlotskii, and D. L. Rakhmankulov, *Rus. J. Appl. Chem.,* 1990, **63**, 226.
70. H. Maeda, T. Kukue, Y. Nakatsuyi, and M. Ohara, *J. Org. Chem.*, 1982, **47**, 5167.
71. I. G. Ovchinnikova, O. V. Fedorova, and G. L. Rusinov, *Russ. J. Org. Chem.*, 1999, **35**, 1082.
72. P. D. Beer, Zh. Chen, A. Grieve, and J. Haggitt, *J. Chem. Soc., Chem. Commun.,* 1994, 2413.
73. E. I. Ivanov, A. A. Politchuk, and G. D. Kalayanov, *Chem. Heterocycl. Compd.* (Engl. Transl.), 1992, **28**, 1074.
74. E. I. Ivanov, *Chem. Heterocycl. Compd.* (Engl. Transl.), 1998, **34**, 723.
75. S. F. Duggan, G. Fallon, S. J. Langford, V.-L. Lau, J. F. Satchell, and M. N. Paddon-Pow, *J. Org. Chem.,* 2001, **66**, 4419.
76. S. V. Klyatskaya, E. V. Tretyakov, and S. F. Vasilevsky, *Russ. Chem. Bull.*, 2002, 128.
77. S. V. Klyatskaya and E. V. Tretyakov, Book of Abstracts of Youth School on the Organic Chemistry, Novosibirsk, 2001, 135.
78. M. Tada, H. Hamazaki, and H. Hirano, *Chem. Lett.,* 1980, 921.
79. H. Hirano, R. Li, and M. Tada, *J. Heterocycl. Chem.*, 1982, **19**, 1409.
80. M. Tada, H. Hamazaki, and K. Tsuzuki, *J. Heterocycl. Chem.,* 1985, **22**, 977.
81. G. L. Rusinov, N. A. Itsikson, D. G. Beresnev, and O. N. Chupakhin, *Heterocyclic Comm.*, 2002, 73.
82. J. E. Redman, P. D. Beer, S. W. Dent, and M. G. B. Drew, *Chem. Commun.*, 1998, 231.
83. Zh. Ge, Yu. Li, Zh. Guo, Zh. Shi, and D. Zhu, *Tetrahedron Lett.*, 1999, **40**, 5759.
84. Yu. V. Fedorov, O. A. Fedorova, N. E. Shepel, E. N. Andryukhina, S. P. Gromov, and M. V. Alfimov, Book of Abstract the Second International Symposium "Molecular design and synthesis of supramolecular architectures", Kazan, 2002, 153.
85. S. P. Gromov and M. V. Alphimov, *Russ. Chem. Pharm. Bull.,* 1997, **46**, 611.
86. V. I. Dulenko, S. L. Bogza, and Yu. A. Nikolyukin, *Chem. Heterocycl. Compd.* (Engl. Transl.), 1283.
87. N. Iqbal and Y. Ueno, *Monatsh. Chem.*, 1992, 123, 199.
88. F. Fernāndez-Lāzaro, A. Sastre, and T. Torres, *J.Chem.Soc., Chem.Commun.,* 1995, 419.
89. G. L. Rusinov, D. G. Beresnev, and O. N. Chupakhin, *Russ. J. Org. Chem.*, 1998, **34**, 423.
90. O. N. Chupakhin, G. L. Rusinov, D. G. Beresnev, and H. Neunhoeffer, *J. Heterocycl. Chem.*, 1997, **34**, 573.
91. O.N. Chupakhin, G.L. Rusinov, D.G.Beresnev, and N.A.Itsikson, *Russ. J. Org. Chem.*, 35, 1253.
92. O. N. Chupakhin, V. N.Charushin, and H. C.van der Plas, 'Nucleophilic Aromatic Substitution of

Hydrogen', 'Academic Press', San Diego, 1994.
93. V. N. Charushin, O. N. Chupakhin, and H. C. van der Plas, *Adv. Het. Chem.*, 1988, 301.
94. D. G. Beresnev and O. N. Chupakhin, *Russ.Chem. Rev.*, 2002, 707.
95. N. A. Itsikson. 'Direct C-C coupling of hetarenes with macrocycles (nucleophilic attack on unsubstituted carbon atom in azines)', Ph. D. Thesis, Ekaterinburg, 2003.
96. G. L. Rusinov, D. G. Beresnev, N. A. Itsikson, and O. N. Chupakhin, *Heterocycles,* 2001, **55**, 2349.
97. A. Prassanna de Silva, H. Q. N. Gunaratnez, Th. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, and T. E. Rice, *Chem. Rev.*, 1997, **97**, 1515.
98. T. R. Akopyan and E. G.Paronikyan, *Chem. Heterocycl. Compd.* (Engl. Transl.), 1997, **33**, 1466.
99. V. V. Voronin and E. N.Ulomsky, Book of Abstracts of Youth Scientific School on Organic Chemistry, Novosibirsk, 2001, 81.
100. A. A. Kalinin, O. G. Isaykina, and V. A. Mamedov, Book of Abstracts the Second International Symposium "Molecular design and synthesis of supramolecular architectures", Kazan, 2002, P-18.
101. V. A. Mamedov, A. A. Kalinin, A. T. Gubaidullin, E. A. Gorbunova and I. A. Litvinov, Book of Abstracts the Second International Symposium "Molecular design and synthesis of supramolecular architectures", Kazan, 2002, P-102.
102. C. F. Martens, A. P. H. J. Schenning, R. J. M. K. Gebbink, M. C. Feiters, J. G. M. van der Linden, J. Heck, and R. J. M. Nolte, *J. Chem. Soc., Chem. Commun.*, 1993, 88.
103. E. G. Mesropyan, G. B. Ambartsumyan, and A. A. Avertisyan, *Russ. J. Org. Chem.*, 1998, **34**, 104.
104. M. V. Martinez-Diaz, J. de Mendoza, and T. Torres, *Synthesis*, 1994, 1091.
105. K. Hiratani, S. Aiba, and T. Nakagawa, *Chem. Lett.*, 1980, 477.
106. I.-Ch. Kwon, You. K. Koh, J.-H. Choi, and H.-S. Kim, *J. Heterocycl. Chem.*, 1996, **33**, 1883.
107. A. R. Ahmad, L. K. Mehta, and J. Parrick, *J. Chem. Soc., Perkin Trans.1,* 1996, 2443.
108. M. I. Rodrīguez-Franco, P. San Lorenzo, A. Martínez, and P. Navarro, *Tetrahedron,*1999, **55**, 2763.
109. T. V. Nikitina and D. N. Kozhevnikov, Book of Abstracts of Youth Scientific School on the Organic Chemistry, Ekaterinburg, 2000, 253.
110. J. Arrowsmith, Sh.A. Jennings, D. A. F. Langnel, R. T. Wheelhouse and M. F. G. Stevens, *J. Chem. Soc, Perkin Trans.1*, 2000, 4432.
111. S. Kumar, R. Saini, and H. Singh, *J. Chem. Soc., Perkin Trans.1*, 1992, 2011.
112. O. V. Fedorova, M. S. Zhidovinova, G. L. Rusinov, and I. G. Ovchinnikova, *Russ. Chem. Bull.*, 2003, in press.
113. G. L. Rusinov, N. A. Itsikson, D. G. Beresnev, O. V. Fedorova, I. G. Ovchinnikova, and O. N. Chupakhin, *J. Inclusion Phen.*, 2003 – in press.
114. A. G. Korenin, P. V. Galkin, N. M. Glushakova, V. P. Lodygina, I. L. Eremenko, S. E. Nefedov, and L. T. Eremenko, *Russ.Chem. Bull.*, 2001, 1553.
115. O. V. Fedorova, G. L. Rusinov, M. S. Zhidovinova, I. G. Ovchinnikova, and O. N. Chupakhin, Book of Abstracts the Second International Symposium "Molecular design and synthesis of supramolecular

architectures", Kazan, 2002, P-92.
116. X. Zeng, L. Weng, L. Chen, X. Leng, H. Ju, X. He, and Zh.-Zh. Zhang, *J. Chem. Soc., Perkin Trans. 2,* 2001, 545.
117. A. F. Danil de Namor, O. E. Piro, L. E. Pulcha Salazar, A. F. Aguilar-Cornezo, N. Al-Rawi, E. E. Castellano, and F. J. Sueros Velarde**,** *J. Chem. Soc., Faraday Trans.,* 1998, **94**, 3097.
118. T. Yamato, M. Haraguchi, J.-Ich. Nishikawa, and S. Ide, *J. Chem. Soc., Perkin Trans. 1,* 1998, 609.
119. A. Casnati, C. Fischer, M. Guardigli, A. Isernia, I. Manet, N. Sabbatini, and R. Ungaro, *J. Chem. Soc., Perkin Trans. 2,* 1996, 395.
120. P. D. Beer, Zh. Chen, A. J. Coulden, A. Grieve, D. Hesek, F. Szemes, and T. Wear, *J. Chem. Soc., Chem. Commun.,*1994, 1269.
121. P. D. Beer and J. B. Cooper, *J. Chem. Soc., Chem. Commun.,* 1998, 129.
122. P. D. Beer, V. Timoshenko, M. Maestri, P. Passaniti, and V. Balzani, *Chem. Commun.,* 1999, 1755.
123. P. D. Beer, M. G. B. Drew, D. Hesek, M. Shade, and F. Szemes, *Chem. Commun.*, 1996, 2161.
124. J.-B. Regnouf-de-Vains and R. Lamartine, *Helv. Chem. Acta*, 1994, **77**, 1817.
125. G. Ulrich, R. Ziessel, I. Manet, M. Guardigli, N. Sabbatini, F. Fraternali, and G. Wipff, *Chem. Eur. J,* 1997, **3**, 1815.
126. N. Psychogios and J.-B. Regnouf-de-Vains, *Tetrahedron Lett.*, 2001, **42**, 2799.
127. A. F. Danil de Namor, E. E. Castellano, L. E. Pulcha Salazar, O. E. Piro, and O. Jafou, *Phys. Chem. Chem. Phys.*, 1999, **1**, 285.
128. F. Arnaud-Neu, G. Ferguson, S. Fuandswasdi, A. Notti, S. Pappalardo, M. F. Parisi, and A. Petringa, *J. Org. Chem.*, 1998, **63**, 7770.
129. U. Lüning, F. Löffler, and J. Eggert, 'Selective modifications of calix[6]arenes. Chapter 4 in Calixarenes 2001,' ed. by Z. Asfari, V. Boemer, J. Harrowfield, and J. Vicens, 'Kluwer Academic Publishers', Netherlands, 2001.
130. D. M. Rudkevich, 'Self-assembly in solution. Chapter 8 in Calixarenes 2001', ed. by Z. Asfari, V. Boemer, J. Harrowfield, and J. Vicens, 'Kluwer Academic Publishers'. Netherlands, 2001.
131. Z.-T. Li, G. Z. Ji, C.-X. Zhao, S.-D. Yuan, H. Ding, C. Huang, A.-L. Du, and M. Wei, *J. Org. Chem.*, 1999, **64**, 3572.
132. S. Pellet-Rostaing, J.-B. Regnouf-de-Vains, and R. Lamartine, *Tetrahedron Lett.,* 1996, **37**, 5889.
133. T. Yamato, F. Zhang, K. Kumamaru, and H. Yamamoto, *J. Inclusion Phen.*, 2002, **42**, 51.
134. W. Sliwa, *Heterocycles,* 2001, **55**, 181.
135. U. Lüning, Book of Abstracts the 6th International Conference "Calixarenes 2001", Enschede, 2001, SL-9.
136. H. Ross and U. Lüning, *Angew. Chem.,*1995, **107**, 2723.
137. A. P. Marchand, H.-S. Choug, M. Takhi, and T. D. Power, *Tetrahedron,* 2000, **56**, 3121.
138. G. Ulrich and R. Ziessel, *Tetrahedron Lett.*, 1994, **35**, 6299.
139. M. Saadioui and V. Böhmer, 'Double- and multi-calixarenes. Chapter 7 in Calixarenes 2001', ed. by Z.

Asfari, V. Boemer, J. Harrowfield, and J. Vicens, 'Kluwer Academic Publishers'. Netherlands, 2001.

140. X. Zeng, L. Weng, l. Chen, F. Xu, Q. Li, X. Leng, X. He, and Zh.-Zh. Zhang, *Tetrahedron,* 2002, **58**, 2647.
141. D. Hessek, Yo. Inoue, S. R. L. Everitt, M. Kunieds, H. Ishida, and M. G. B. Drew, *Tetrahedron: Asymmetry*, 1998, **9**, 4089.
142. P. D. Beer, M. G. B. Drew, and K. Gradwell, *J. Chem. Soc., Perkin Trans. 2*, 2000, 511.
143. Ya. Molard., C. Bureau, H. Parrot-Lopez, R. Lamartine, and J.-B. Reghouf-de-Vains, *Tetrahedron Lett.,* 1999, **40**, 6383.
144. A. Hamdi, R. Abidi, M. Trabelsi Ayadi, P. Thuery, M. Nierlich, Z. Asfari, and J. Vicent, *Tetrahedron Lett.,* 2001, **42**, 3595.
145. J. B. Cooper, M. G. B. Drew, and P. D. Beer, *J. Chem. Soc., Dalton Trans.,* 2001, 392.
146. E. A. Alekseeva, V. A. Bacherikov, A. I. Gren, A. V. Mazepa, V. Ya. Gorbatyuk, and S. P. Krasnotchekaya, *Russ. J. Org. Chem.,* 2000, **36**, C.1321.
147. E. A. Alekseeva, S. P. Krasnorchekaya, and A. I. Gren, *Russ. J. Gen. Chem.*, 2002, **72**, 166.
148. Q.-Yu. Zheng, Ch.-Ch. Zeng, Ya.-L. Tang, and Zh.-T. Huang**,** *Book of Abstracts the 6th International Conference "Calixarenes 2001"*, Enschede, 2001, P-64.
149. W. Jaunky, M. W. Hosseini, J. M. Planeix, A. de Cian, N. Kyritsakas, and J. Fischer, *Chem. Commun.*, 1999, 2313.
150. H. Deligoz and N. Ercan, *Tetrahedron,* 2002, **58**, 2881.
151. Yu. Yu. Morzherin and T. V. Glukhareva, Book of Abstracts the 6th International Conference "Calixarenes 2001", Enschede, 2001, P-76.
152. K. Imamoto, K. Avaki, H. Fujishima, and S. Shinkai, *J. Chem. Soc., Perkin Trans.1*, 1992, 1885.
153. J.-B. Regnouf-de-Vains, and R. Lamartine, *Tetrahedron Lett.,* 1996, **37**, 6311.
154. P. Molenveld, J. E. J. Engbersen, H. Kooijman, A. L. Spek, and D. N. Reinhoudt, *J. Am. Chem. Soc.,* 1998, **120**, 6726.
155. P. Molenveld, J. F. J. Engbersen, and D. N. Reinhoudt, *J. Org. Chem.,* 1999, **64**, 6337.
156. G. Dospil and J. Schatz, *Tetrahedron Lett.*, 2001, **42**, 7837.
157. M. Baur, G. Dospil, and J. Schatz, Book of Abstracts the 6th International Conference "Calixarenes 2001", Enschede, 2001, P-12.
158. C. D. Gutsche, B. Dhawan, J.A. Levine, K.H. No, and L. J. Bauer, *Tetrahedron,* 1983, **39**, 409.
159. S. Pellet-Rostaing, J.-B. Regnouf de Vains, and R. Lamartine, *Tetrahedron Lett.*, 1995, **36**, 5745.
160. F. C. Tucci, D. M. Rudkevich, and Jr. J. Reber, *J. Org. Chem.,* 1999, **64**, 4555.
161. R. N. Warrener, D. N. Butler, and R. A. Russel, *Syn. Lett.,* 1998, 566.
162. W. Sliwa, G. Matusiak, and M. Deska, *Heterocycles,* 2002, **57**, 2179.

163. M. H. B. Grote Gansey, F. K. G. Bakker, M. C. Feiters, H. P. M. Geurts, W. Verboom, and D. N. Reinhoudt, *Tetrahedron Lett.,* 1998, **39**, 5447.
164. O. N. Chupakhin, G. L. Rusinov, N. A. Itsikson, D. G. Beresnev, I. N. Nikolaeva, A. R. Burilov, and A. I. Konovalov, *Heterocyclic Comm.*, 2003.- in press.