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Synthesis of *N*-tetrasubstituted cyclam derivatives appended with sulfonyl or sulfinyl groups via aza-Michael addition

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Abstract—Azamacrocycles bearing four arylsulfonyl or arylsulfinyl pendant arms have been synthesised with good yields through nucleophilic addition of 1,4,8,11-tetraazacyclotetradecane (cyclam) to phenylvinylsulfone, phenylvinylsulfoxide or (*R*)-tolylvinylsulfoxide in isopropanol/water media. The crystal structure of the tetraethylsulfonylphenyl substituted macrocycle has been determined by X-ray crystallography. Preliminary studies of the coordination properties of these functionalised macrocyles towards Cu(II) and Eu(III) indicate that pendant sulfoxide groups act as oxygen donor coordinating groups.

1. Introduction

Macrocyclic ligands and in particular polyazamacrocycles have received a great deal of research interest since they find various applications in numerous fields such as coordination chemistry, biomedical uses, ion sequestration and extraction or catalysis.[1–7] Among them, cyclam (1,4,8,11-tetraazacyclotetradecane) has attracted a widespread attention owing to its high affinity for transition metals.[1–6,8] Numerous cyclam derivatives have been reported and the presence of additional functionalities on one or several pendant arms has been found to enlarge the recognition and complexation properties.[1–6,9–14] The grafting of pendant arms has also been used to modulate the solubility as well as the solution behaviour: cyclam derivatives with appended perfluorinated tails have been used as ligands in fluorous biphasic catalysis,[15,16] macrocyclic surfactants have been designed by linking amphiphilic groups onto the cyclam.[17,18]

Functionalisation of cyclam is usually performed by N-alkylation of its secondary amines via nucleophilic substitution with halogenated or tosylated reagents. Alternatively, some cyclam derivatives have been obtained through nucleophilic additions of cyclam to Michael acceptors:[13,15,17,19–22] among them reactions with acrylic derivatives (like acrylonitrile, acrylic esters or acrylamides) have been the most widely studied and used to obtain a variety of appended cyclam derivatives.[17,19–22]

Vinyl- and alkenylsulfones and sulfoxides are excellent Michael acceptors and have been found to react with a number of nucleophiles.[23–35] Among them vinyl- and divinylsulfones have been the most widely studied and aza-Michael additions to vinylsulfones have proven to be useful synthetic tools for the functionalisation of various amines[15,24–32] as well as in the synthesis of nitrogen heterocycles.[33] Except for the reaction of cyclam with divinylsulfone, that has been found to lead to a 1,8-*N*,*N*-bisethylsulfonyl bridged macrocycle,[30] and with perfluorinated acceptors,[15] the synthesis of cyclam derivatives with appended sulfinyl or sulfonyl groups, through aza-Michael additions, has never been investigated before. We anticipated that conjugate additions of cyclam to vinylsulfones or sulfoxides would give a straightforward access to new families of *N*-ethylsulfinyl and *N*-ethylsulfonyl substituted macrocycles. Such functionalised cyclam derivatives may present interesting binding properties since the appended SO groups may act as auxiliary ligands in the formation of coordination complexes. Furthermore, reaction with enantiomerically pure vinylsulfoxides could give access to optically active ligands or organocatalysts usable in asymmetric catalysis. Moreover, electrophilic substitutions in the alpha-position to the sulfonyl groups, well known and widely used in the chemistry of β-aminosulfones,[25] might permit further functionalisations.

Herein, we describe the straightforward synthesis of *N*-tetrasubstituted cyclam derivatives with ethylarylsulfonyl and

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ethylarylsulfinyl pendant arms, via aza-Michael additions as well as preliminary studies of their coordination properties towards Cu(II) and Eu(III).

2. Results and discussion

2.1. Synthesis of the *N*-tetrasubstituted macrocycles appended with sulfinyl and sulfonyl groups

The synthesis of tetrasubstituted macrocycles was investigated via nucleophilic addition of cyclam to phenyl vinyl sulfone **1**, phenyl vinyl sulfoxide **2** as well as to the enantiomerically pure (*R*)-*p*-tolyl vinyl sulfoxide **3** (Scheme 1). The latter has been prepared via the nucleophilic substitution of vinyl magnesium bromide on (*S*) menthyl-*p*-toluenesulfinate following Kagan's experimental conditions.[36]

The reactions were performed with an excess of Michael acceptors in protic solvents. The different sets of experimental conditions tested are summarised in Table 1.

The choice of the solvent *i*-PrOH or *i*-PrOH/water was made according to published results that demonstrated that hetero-Michael additions are favoured in protic medium with remarkable rate accelerations in water presumably due to a faster proton transfer.[17,37] For instance in the case of sulfinyl and sulfonyl substituted acceptors, addition of amines to vinylsulfoxide and vinylsulfone derivatives was found to be faster in ethanol than in benzene[28,34] and reaction of isobutylamine with a bis-vinylsulfone acceptor proceeded in methanol but did not occur in chloroform.[31] In the formation of bridged macrocycles involving aza-Michael additions to divinylsulfone, best results were obtained in protic media (isopropanol or isopropanol/water).[30] Furthermore, we recently found that addition of the amines of cyclam to perfluorinated Michael acceptors is readily achieved in an *i*-PrOH/water medium.[15]

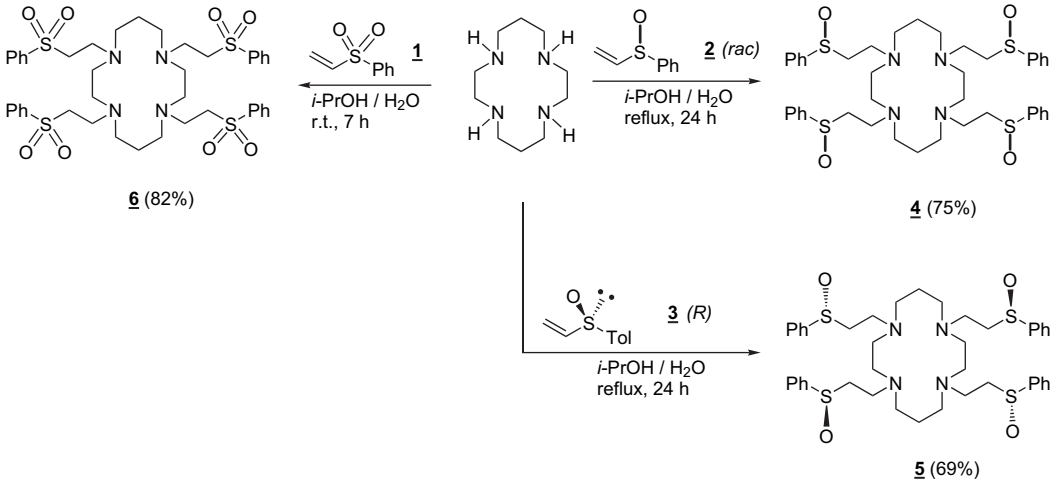
In the present case, the reaction of cyclam with a slight excess of phenyl vinyl sulfoxide **2** (5 equiv per cyclam) proceeded sluggishly in isopropanol and the reaction rate significantly increased in isopropanol/water (Table 1, entries 1–3). Heating up the reaction mixture improved the yield and best conversions were obtained at 65 °C. The tetrasubstituted macrocycles **4** and **5** have been isolated after purification by column chromatography in 70–75% yields from **2** and **3** (Table 1, entries 4,5). These experimental conditions within this range of temperatures do not induce racemisation of the sulfinyl groups since the optical activity of the macrocycle **5** is the same as when the reaction was run at room temperature (Table 1, entries 5,6). The tetrasubstituted macrocycles **4** and **5** have been fully characterised. Elemental analyses and mass spectra confirmed the grafting of four arylethylsulfinyl pendant arms. The observed number of ^{1}H and ^{13}C NMR signals and the relative integration of the corresponding ^{1}H signals are in agreement with the tetrasubstitution pattern.

Table 1. Reaction conditions for the synthesis of sulfinyl and sulfonyl appended macrocycles **4–6**

Entry	Michael acceptor	Solvent	*T*/°C	Reaction time	Product	Yield/%
1	**2** (5 equiv)[a]	*i*-PrOH	rt	3 days	**4**	16[b]
2	**2** (5 equiv)[a]	*i*-PrOH/H_2O (2/1)	rt	24 h	**4**	56[b]
3	**2** (5 equiv)[a]	*i*-PrOH/H_2O (2/1)	rt	5 days	**4**	55[b]
4	**2** (5 equiv)[a]	*i*-PrOH/H_2O (2/1)	65	24 h	**4**	75[b]
5	**3** (5 equiv)[a]	*i*-PrOH/H_2O (2/1)	65	15 h	**5**	69[b,d]
6	**3** (5 equiv)[a]	*i*-PrOH/H_2O (2/1)	rt	15 h	**5**	13[b,d]
7	**1** (6 equiv)[a]	*i*-PrOH/H_2O (2/1)	rt	17 h	**6**	68[c]
8	**1** (10 equiv)[a]	*i*-PrOH/H_2O (2/1)	rt	7 h	**6**	82[c]

[a] Number of equivalent per cyclam.
[b] Isolated yield after purification by column chromatography.
[c] Isolated yield after recrystallisation.
[d] The optical rotation is identical for the products obtained at 65 °C or at rt.

The tetrasubstituted macrocycle **6** with sulfonyl pendant arms was obtained similarly from phenyl vinyl sulfone **1** (Table 1, entries 7,8). The reaction went to completion at room temperature provided that an excess of Michael acceptor (6–10 equiv per cyclam) was used. Room temperature reaction of cyclam with phenyl vinyl sulfone **1** proceeds more rapidly than with aryl vinyl sulfoxides **2** and **3**, in agreement with the known higher reactivity of a double bond activated with a sulfone compared to that substituted with a sulfoxide.[24–26] The macrocycle **6** conveniently precipitated out of the reaction mixture and was crystallised by slow diffusion of methanol through a chloroform solution of **6** in



Scheme 1. Synthesis of sulfinyl and sulfonyl appended macrocycles **4–6**.