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Efficient highly stereoselective synthesis of olefinic macrocyclic crown-formazans with the *Z*-configuration via ring-closure metathesis

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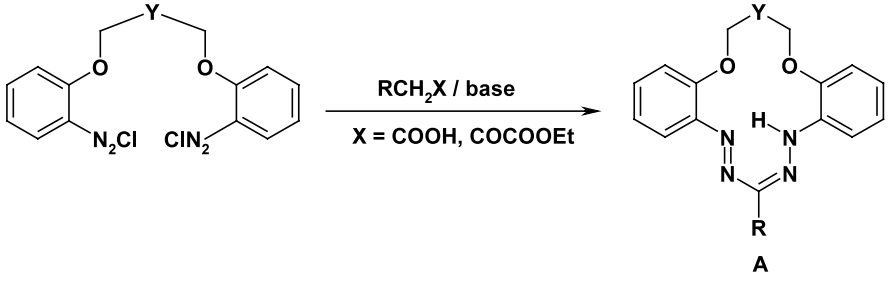
Abstract—RCM of 1,5-bis-*o*-allyloxyphenylformazans with the suitably located 1,ω-dienes leads to an efficient, highly stereoselective, synthetic approach towards *Z*-olefinic 15-membered ring macrocyclic crown-formazans with potential applications. A novel reduction of pyridine *N*-oxides to pyridines by the action of Grubbs' catalyst has been discovered.

The chemistry and diverse applications of formazans and crown-formazans (tetra-azacrown compounds) have received much attention and are the subject of a large number of reviews that have been cited previously.[1a–c] Many crown-formazans **A** have been synthesized and depending on the substituent Y show important high selectivity towards certain metal ions. Thus, with Y = CH_2, CHOH, C=CH_2, 1,2-C_6H_4, compounds **A** exhibit high lithium selectivity in spectrophotometric determinations, however, their incorporation as neutral ionophores in ion selective electrodes gave a good cesium ion selective electrode.[1d–f] Recently a range of these crown-formazans were prepared and the effect of the R group on the selectivity was reported. Selectivity was enhanced with R = cyano, nitro and 4-pyridyl *N*-oxide.[1c–e] Other crown-formazans **A** with larger ring sizes [Y = $(CH_2OCH_2)_n$, n = 0–2] were reported to be useful for selective extraction of Cu and Hg ions.[1g–i] Thus, crown-formazans are among the recently developed classes of neutral ionophores which are useful in measurements of intracellular as well as extracellular cation concentration and their transport phenomena through membranes and in solvent extractions are subjects of considerable current interest.[2] All feasible reported synthetic approaches towards crown-formazans depend mainly on coupling of a bis-diazonium salt with active methylene compounds (Scheme 1) with yields not exceeding 10% in most cases with the need of high dilution conditions and a template effect.[1]

Recently, ring-closing metathesis (RCM) has been widely used as a versatile technique for the formation of cyclic olefins with an increasing number of applica-



Scheme 1.

Keywords: ring-closure metathesis; 1,ω-dienes; 1,5-bis-*o*-allyloxyphenylformazans; dibenzo[*b*,*i*]-1,11-dioxa-4,5,7,8-tetraazacyclopentadeca-2,4,6,9,13-pentaene; reduction; Grubbs' catalyst; pyridine *N*-oxides.

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tions which has been reviewed recently and cited in our recent publication.[3] The atom economic efficient application of the commercial available Grubbs' catalysts **I** for the synthesis of some crown[4] and azacrown[3,5] compounds encouraged us to extend this methodology to the synthesis of crown-formazans.

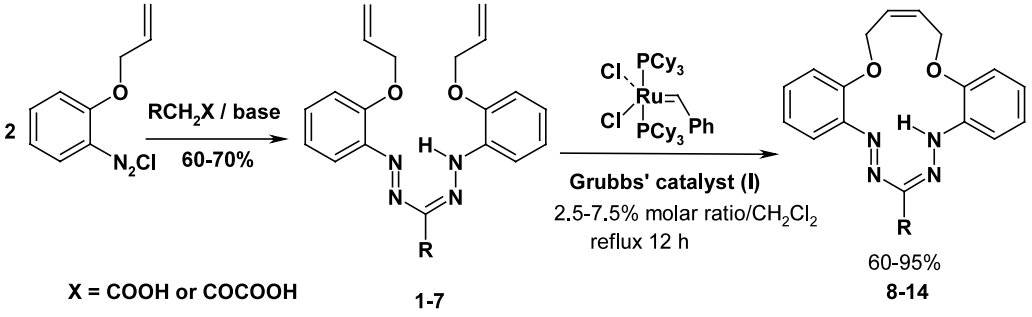
In the present work we report our investigations on the application of RCM with catalyst **I** as the key macrocyclization step in the synthesis of macrocyclic crown-formazans. Results obtained in this work (Table 1) provide efficient atom economic synthetic approaches towards macrocyclic crown-formazans incorporating an olefinic double bond inside the macrocyclic ring with potential applications in supramolecular chemistry.

Scheme 2 illustrates our synthetic route starting from the readily available *o*-allyloxybenzenediazonium chloride obtained from *o*-allyloxyaniline hydrochloride[6] which is then coupled with the appropriate active methylene compound to give 60–70% yields of the corresponding 1,5-bis-*o*-allyloxyphenyl-3-substituted formazans **1**–**7**. RCM of the latter dienes proceeded under mild conditions using 2–7.5 mol% of **I** in refluxing CH_2Cl_2 to give high yields of the corresponding crown-formazans (Table 1). In contrast to other syn-

Table 1.

Run	Substrate[d]	Yield (%)[d]	Product[e]	R_f (substrate/product)[f]	^{1}H NMR of Z/E products[g]		
			Z:E% ratio		NH	OCH_2	OCH$_2$$CH$=
1	**1**	20,[a] 40,[b] 60[c]	**8**	0.85/0.7 (i)	15.97	4.79	6.33
			93:7		15.97	4.63	6.33
2	**2**	40,[a] 65[b]	**9**	0.82/0.68 (ii)	15.75	4.84	6.32
			96:4		13.50	4.72	6.32
3	**3**	60,[a] 95[b]	**10**	0.63/0.46 (iii)	15.76	4.84	6.33
			96:4		13.55	4.72	6.33
4	**4**	20,[a] 60[b]	**11**	0.64/0.5 (iii)	15.69	4.81	6.29
			97:3		13.40	4.72	6.29
5	**5**	20,[a] 60[b]	**12**	0.37/0.27 (iii)	15.60	4.83	6.32
			97:3		13.42	4.71	6.32
6	**6**	5,[a] 8,[b] 10[c]	**13**	0.23/0.2 (iv)	15.93	4.82	6.35
			95:5		16.45	4.72	6.35
		5,[a] 10,[b] 15[c]	**15**	0.23/0.37 (iv)	16.10	4.82	6.35
			95:5		16.10	4.72	6.35
		10,[a] 15,[b] 35[c]	**16**	0.23/0.4 (iv)			
7	**7**	40,[a] 90[b]	**14**	0.5/0.25 (v)	15.52	4.77	6.29
			90:10		13.15	4.66	6.21
8	**13**	80[c]	**15**	0.2/0.37 (iv)			
			95:5				
9	**16**	40[c]	**15**	0.4/0.37 (iv)			
			95:5				

[a] Substrate (0.01 M), Grubbs' catalyst **I** (2.5 mol%); CH_2Cl_2, reflux 12 h.
[b] Substrate (0.01 M), **I** (5 mol%); CH_2Cl_2, reflux 12 h.
[c] Substrate (0.01 M), **I** (7.5 mol%); CH_2Cl_2, reflux 12 h.
[d] The yield was determined by 400 MHz ^{1}H NMR, unreacted starting substrates account for most of the remaining percent in each case.
[e] All substrates and products were analyzed by ^{1}H, ^{13}C NMR, GC–MS, and gave satisfactory elemental analysis.
[f] Merck Al-silica gel 60F_{254}. Elution solvents are as follows: (i) 50/50 EtOAc/pet. ether (40–60); (ii) 20/80/0.3 DCM/pet. ether (40–60)/MeOH; (iii) 20/80/1 DCM/pet. ether (40–60)/MeOH; (iv) 80/15/5 DCM/pet. ether (40–60)/MeOH; (v) 30/70 EtOAc/pet. ether (40–60).
[g] All NMR spectra were measured in $CDCl_3$, NH (sharp singlet), OCH_2 (m), OCH$_2$$CH$= (m).



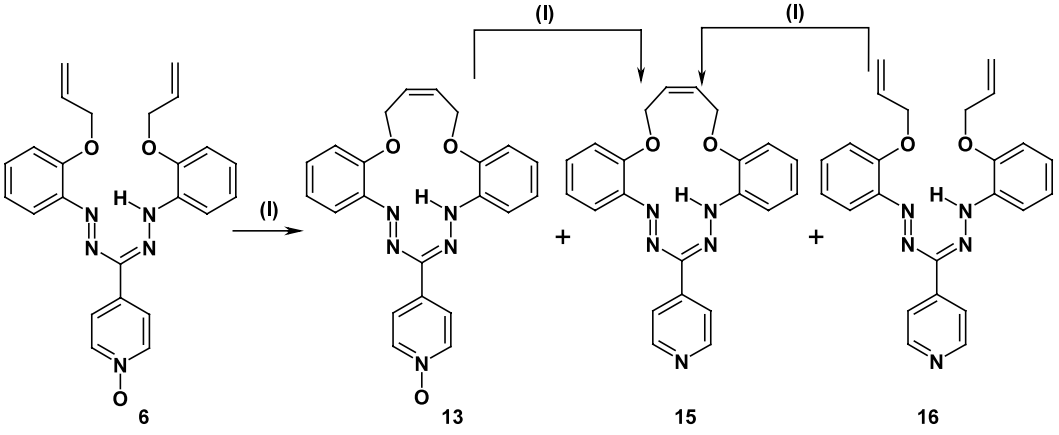
Scheme 2.

thetic procedures (Scheme 1) where the by-products are waste polymeric materials, the present RCM methodology yields only the desired crown-formazans in addition to recyclable starting materials in almost quantitative molar ratios.

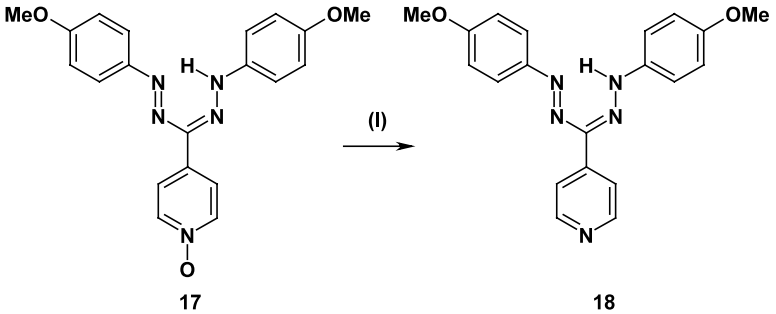
Interestingly in case of the pyridyl *N*-oxide derivative **6** RCM macrocyclization gave, in addition to the expected product **13**, the corresponding deoxygenated compounds **15** and **16** (Scheme 3). RCM of **16** gave the expected crown-formazan **15**. The reduction behaviour of **I** towards pyridine *N*-oxide was further investigated by heating **13** with **I** (7.5 mol%) in refluxing methylene chloride for 2 h whereby the corresponding pyridyl derivative **15** was obtained in 80% yield. Reduction of other acyclic formazans substituted with 3-(4-pyridyl *N*-oxide) by the action of **I** was investigated, e.g. **17** gave the deoxygenated derivative **18** (Scheme 4). The reductive catalytic utility of **I** towards other pyridine *N*-oxides is currently under further investigation and the results will be reported separately.

The major product in all the RCM reactions presented here was shown to be the *Z* isomer with the characteristic ^{13}C signal of the OCH_2 (of the $OCH_2CH{=}CHCH_2O$) at ca. $\delta = 63$. On the other hand the ^{13}C signal of the OCH_2 of *E* isomers appears more upfield at around $\delta = 70$. The highly stereoselective *cis* double-bond formation was readily determined by the OCH_2 ^{13}C NMR chemical shift, which appears more downfield in the ^1H NMR and more upfield in the ^{13}C NMR than for the *trans* isomer. Full ^1H and ^{13}C NMR spectra of representative examples are given.[7,8] It is interesting to note that the presence of the formazan moiety inside the ring enhanced considerably the stereoselectivity of the newly formed double bond in favour of the *cis* geometry. This is in contrast to the RCM synthesis of crown ethers, azacrowns and crown-diamides where the *trans* geometry competes considerably and is even more favoured in many cases.[3–5] Moreover, the present investigation presents interesting examples of stereoselective *Z* macrocyclic olefin formation most probably controlled largely by the rigidity and planarity of the diarylformazan moiety that becomes, at the end, a part of the macrocyclic crown-formazan.

The present work demonstrates the efficient application of RCM techniques for the synthesis of crown-formazan derivatives with potential diverse applications in supramolecular chemistry and as starting compounds for further synthetic transformations. Moreover, examples of RCM presented here offer one of the best known, highly stereoselective, synthesis of crown-formazans containing *cis*-double bonds. It also, expands the utility of RCM methodology and its application to the synthesis of cyclic olefins of large ring sizes with the good tolerance of Grubbs' catalyst **I** to additional functional groups. Applications of this method to the synthesis of other functional derivatives of crown compounds are currently under active investigation in our laboratory.



Scheme 3.



Scheme 4.

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7. Compound **8**: mp 185–187°C; MS: m/z 333 (M^+, 100%); ^{1}H NMR ($CDCl_3$): δ 4.63 (m, 4H, OCH_2, *E*, 7%), 4.79 (m, 4H, OCH_2, *Z*, 93%), 6.33 (m, 2H, olefinic, *Z*, *E*), 7.08 (t, 2H, $J=8$ Hz), 7.11 (d, 2H, $J=8$ Hz), 7.35 (dt, 2H, $J=1.7$, 8 Hz), 7.86 (dd, 2H, $J=1.7$, 8 Hz), 15.97 (s, 1H, NH, *E*, *Z*); ^{13}C NMR ($CDCl_3$): δ 62.4 (OCH_2), 112.9, 116.5, 122.0, 130.2, 131.5 (5CH), 117.6 (CN), 124.4, 136.3, 151.1 (3C) (*Z*), 70.6 (OCH_2), 116.7, 122.0, 123.1, 129.1, 131.1 (5CH), 118.9 (CN), 129.9, 137.7, 152.8 (3C) (*E*).
8. Compound **14**: mp 220–222°C; MS: m/z 448 (M^+, 100%); ^{1}H NMR ($CDCl_3$): δ 4.66 (m, 4H, OCH_2, *E*, 10%), 4.77 (m, 4H, OCH_2, *Z*, 90%), 6.21 (m, 2H, olefinic, *E*, 10%), 6.29 (m, 2H, olefinic, *Z*, 90%), 7.05 (m, 4H), 7.30 (t, 1H, $J=8.4$ Hz), 7.57 (m, 4H), 7.82 (dd, 2H, $J=1.5$, 8 Hz), 8.14 (dd, 2H, $J=1.4$, 8.4 Hz), 13.15 (s, 1H, NH, *E*), 15.52 (s, 1H, NH, *Z*); ^{13}C NMR ($CDCl_3$): δ 62.6, 112.9, 116.6, 121.9, 128.5, 129.2, 130.3, 131.3, 133.1, 136.7, 140.8, 144.7, 151.2 (*Z*), 71.3, 117.4, 118.4, 123.1, 128.9, 129.6, 130.1, 130.7, 133.3, 139.2, 140.5, 144.0, 152.0 (*E*).