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Study of direct macrocycle formation via the cyclisation of propargyl 2-azidobenzoate

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ABSTRACT

Macrocycles were synthesised via the cyclisation of propargyl 2-azidobenzoate using 'click' chemistry. An LC/MS-based method for the separation of macrocycles is described. In the present work, the influence of various catalysts and reaction conditions on the course of the reaction is evaluated. The reaction is very sensitive to the conditions, and it is demonstrated that it is possible to modify the ratio of macrocycles by varying the reaction conditions. The cyclisation of propargyl 2-azidobenzoate represents an economical method for the preparation of the studied macrocycles.

Macrocyclic molecules are frequently studied due to their unique properties. These molecules are widely occurring and include porphyrins, cyclopeptides and numerous other molecules. Other macrocycles have been synthesised in the laboratory, including cyclophanes, crown ethers and glycophanes. Macrocycles display remarkable biological activities[1,2] or have technical applications. Macrocyclic compounds with triazole rings have been applied as optical and electrochemical chemosensors.[3]

Azidobenzoate **1** is a very reactive starting material that is useful for the preparation of benzoxazepine **7**.[4,5] The reaction is general and can be used for the preparation of derivatives of compound **7**. We demonstrated that compound **1** has limited stability and, at laboratory temperature, partly dimerises to form compound **8**. This reaction is too slow for the routine production of this compound. Therefore, macrocycle **2** formed using this method during the heating of compound **1** (not properly stored) is produced only as an impurity.[5] As macrocyclic compounds of this type can be used in various technical applications, we have developed a general procedure for the synthesis of macrocycles of various ring sizes. The preparation of macrocycles **2**, **3** and **4** was described recently,[6] and consisted of few steps and was laborious. During our work on this problem, we found that azidobenzoate **1** affords a mixture of macrocycles when treated with a copper catalyst. This method represents a simple and attractive strategy for the preparation of these interesting molecules (Scheme 1).[7]

We have developed a simple and effective LC/MS method that makes it possible to quickly compare the results of different experiments.[8]

The structures of the final products were confirmed by HRMS and, in the case of compounds **2**, **3**, **4** and **7** by comparison with a standard. There was also the possibility of formation of linear oligomers **8**, **9** and **10**. We proved recently[6] that these molecules were very reactive and they were not stable under these conditions. The retention times and HRMS of standards **8, 9** and **10** (Fig. 1) are given in Supplementary data to verify the separation possibilities of our analytical method. As we supposed, the linear molecules were not found in the reaction mixture obtained under the conditions of the 'click' reaction.

An example of a separation is presented in Figure 2. The LC/MS analysis of the recently prepared standards is presented in Supplementary data. First, we determined the amount of catalyst necessary for a successful and sufficiently fast reaction. We started with copper sulfate and ascorbic acid, which have been used effectively for the construction of macrocycles in the past.[6] This catalyst however was not effective in a molar amount of approximately 5%.

An acceptable reactivity for compound **1** was obtained with a molar ratio of catalyst to azide of 0.5–1. Under these conditions, the major products were macrocycle **2**, with a yield of approximately 50%, and macrocycle **3**, with a yield of 31%. In addition, macrocycles **4** and **5** were formed. The composition of the reaction mixture did not depend on the quantity of the catalyst. When the

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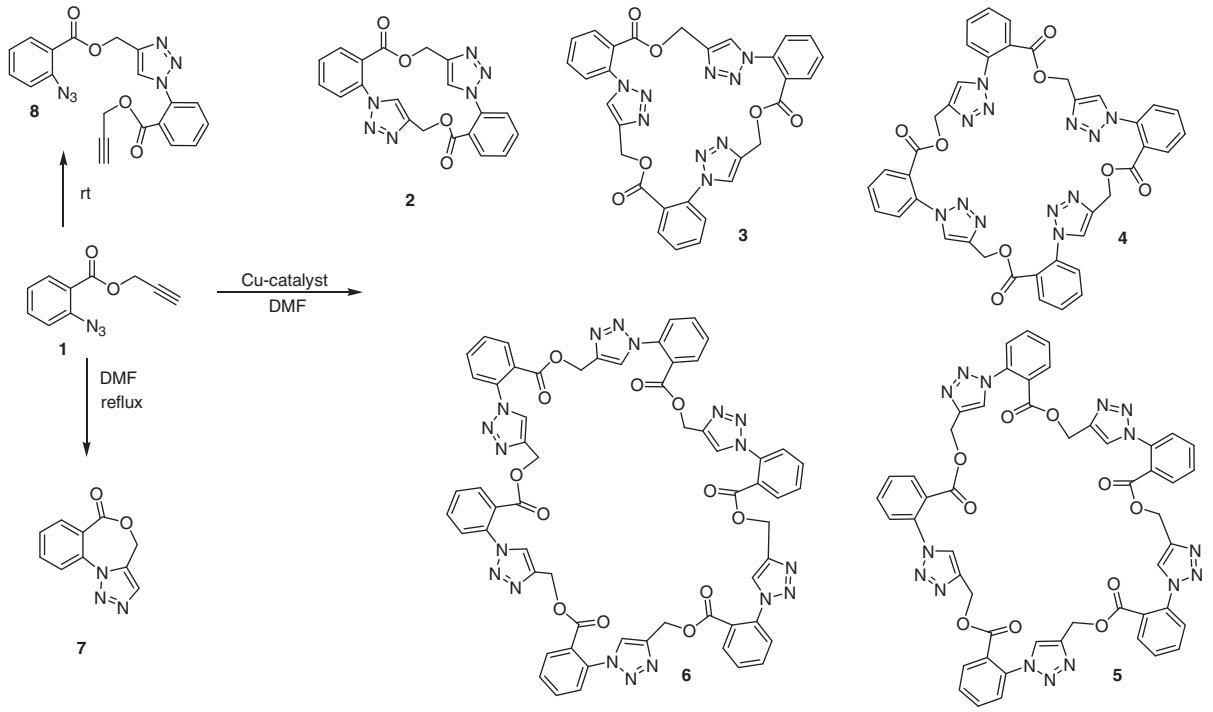

Scheme 1. The mixture of macrocycles formed by the cyclisation of propargyl 2-azidobenzoate.

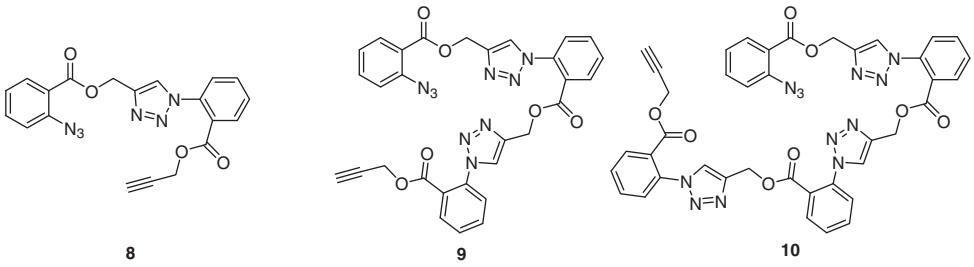

Figure 1. Structures of open oligomers.

solvent was changed to a mixture of water and *N*,*N*-dimethylformamide (DMF), the amount of compound **2** increased to 60%. The influence of temperature on the reaction was unexpected. This influence was studied using a system with copper sulfate and ascorbic acid as catalysts. Higher temperatures had no significant influence on the ratio of the formed products. At a temperature of −15 °C, the production of higher macrocycles **3** and **4** increased (Table 1, entries 5–7). The reaction did not proceed at a temperature of −40 °C. The surprising results were obtained when the catalytic activity of copper(I) halides was tested. If the reaction proceeded, the same products were formed, with the only differences in the proportion of macrocycles in the reaction mixture. The reaction proceeded smoothly if the co-catalyst like *N*,*N*-diisopropylethylamine (DIPEA) or triethylamine (Et_3N) was added to copper(I) chloride or copper(I) bromide. The reaction did not run without one of these co-catalysts. Nevertheless, the reaction catalysed solely by copper(I) iodide was fast. The reaction surprisingly proceeded slower if the mixture of copper(I) iodide and DIPEA was used. Conversely, the reaction rate was fast as the combination of copper(I) iodide with Et_3N was used and it was unexpectedly more selective and afforded 80% macrocycle **2** (Table 1, entries 16–23).

An interesting course of the reaction was observed after the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) being similar in all cases. The reaction was very fast, and the starting material was not observed after 15 min in the reaction mixture. In addition to DBU, macrocycle **2** and an unknown compound were present in the reaction mixture. After a few hours of stirring, the main compounds disappeared, and only DBU and an unknown impurity showing a very small peak were observed in the HPLC chromatogram. The weak catalytic activity of copper(I) chloride or bromide could be explained by their lower solubility in the reaction mixture compared to copper(I) iodide. After the addition of tertiary amines, a solution is formed and reaction is very fast. However, at present we have no explanation for the results of the catalytic activity of the combination of copper(I) halides with DBU and copper(I) iodide with tertiary amines. We are currently working on this problem.

We also tested the influence of copper powder. At room temperature, the reaction was very slow, and after 48 hours, the yields of macrocycle **2** and dimer **8** were only 7% and 21%, respectively (Table 1, entry 25). The rest of the starting material was unchanged. It can be seen from this result that the catalyst was not effective. The formation of product **8** by spontaneous dimerisation of azido derivative **1** was described recently.[5] The extent of the reaction was increased using ultrasound. The influence of ultrasound on heterogenous reactions is commonly known. After 4 h, the starting material was not found in the reaction mixture, and the formation of a mixture of macrocycles was observed (Table 1,

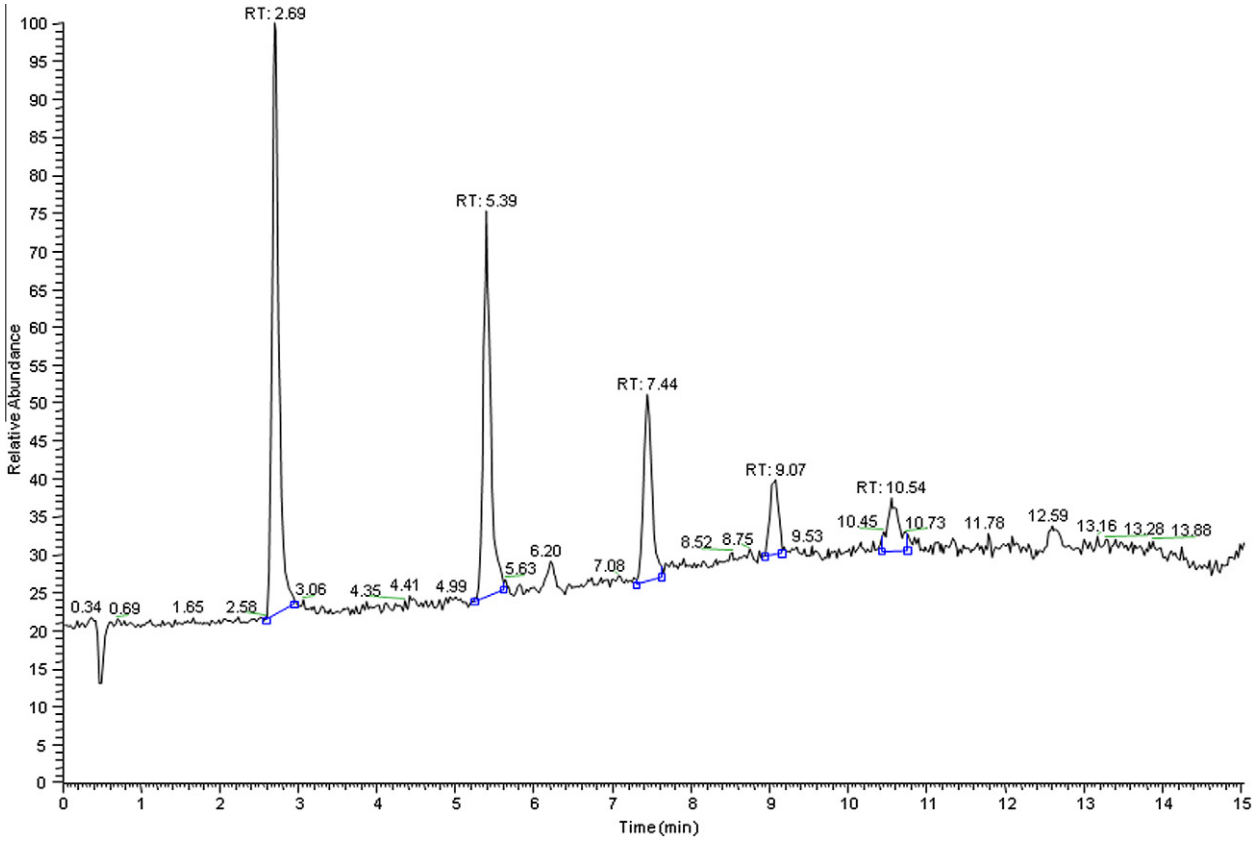

Figure 2. LC/MS method—example of the separation of a reaction mixture.

Table 1
Results of the cyclisation of propargyl 2-azidobenzoate (**1**) under various conditions

Entry	Starting material			Conditions		Products (%)							
	Solvent (mL)	Catalyst (equiv)	Co-catalyst (equiv)	Temp (°C)	Time	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	DMF (0.5)			Reflux	30 min	0	1.8	0	0	0	0	97	0
2	DMF (0.5)	$CuSO_4$ (1)	asc.ac[a] (2.1)	60	15 min	0	52.7	27.6	15.1	4.6	0	0	0
3	DMF (0.5)	$CuSO_4$ (1)	asc.ac[a] (2.1)	25	15 min	0	48.4	31.3	12	8.2	0	0	0
4	DMF (0.5)	$CuSO_4$ (0.5)	asc.ac[a] (1.05)	25	1 h	0	45	31	17.2	6.8	0	0	0
5	DMF (0.5)	$CuSO_4$ (1)	asc.ac[a] (2.1)	−15	4 h	0	29.3	36.8	22.9	7.3	3.6	0	0
6	DMF (0.5)	$CuSO_4$ (0.2)	asc.ac[a] (0.42)	−15	30 h	0	32.5	36	18.8	8	4.6	0	0
7	DMF (2)	$CuSO_4$ (4)	asc.ac[a] (8.4)	−15	5.5 h	0	37.7	36.3	15.3	7.6	3	0	0
8	DMF (0.5)	$CuSO_4$ (1)	asc.ac[a] (2.1)	−25	4 h	37.4	36.4	17	9.1	0	0	0	0
9	DMF (2)	$CuSO_4$ (1.6)	asc.ac[a] (3.36)	−30	2 h	0	41	38.2	16.3	4.5	0	0	0
10	DMF + H_2O (0.15+0.35)	$CuSO_4$ (0.2)	asc.ac[a] (0.42)	25	2.5 h	0	61.9	17.8	10.8	6.2	3.2	0	0
11	DMF + H_2O (0.05 + 0.1)	$CuSO_4$ (0.5)	asc.ac[a] (1.05)	25	15 min	0	59.25	19.15	13	5.4	3.2	0	0
12	MeCN (0.5)	$CuSO_4$ (1)	asc.ac[a] (2.1)	25	6 h	97	0	0	0	0	0	0	0
13	Acetone (0.5)	$CuSO_4$ (1)	asc.ac[a] (2.1)	25	6 h	0	40.7	33.9	11.4	8.8	5.2	0	0
14	EtOH (0.5)	$CuSO_4$ (1)	asc.ac[a] (2.1)	25	6 h	11.8	42.6	25.2	10.4	6.6	3.4	0	0
15	THF (0.5)	$CuSO_4$ (1)	asc.ac[a] (2.1)	25	6 h	31.3	30.9	18.7	5.4	4.5	1.9	0	0

Table 1 (*continued*)

Entry	Starting material			Conditions		Products (%)							
	Solvent (mL)	Catalyst (equiv)	Co-catalyst (equiv)	Temp (°C)	Time	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
16	DMF (0.5)	CuI (0.2)		25	2 h	0	66.2	11.1	4.5	0	0	0	0
17	DMF (0.5)	CuI (0.2)	DIPEA (5)	25	4 h	3.4	51.5	10	6.2	0	0	0	0
18	DMF (0.5)	CuI (0.2)	TEA (5)	25	1 h	1.2	80.2	8.2	4.2	0	0	0	0
19	DMF (0.5)	CuBr (0.2)	DIPEA (5)	25	2 h	0	52.1	30.2	14.1	1.5	0	0	0
20	DMF (0.5)	CuBr (0.2)	Et_3N (5)	25	2 h	0	57.5	22.8	15.7	3.8	0	0	0
21	DMF (0.5)	CuCl (0.5)	Et_3N (5)	25	4 h	0	59.4	28	12.6	0	0	0	0
22	DMF (0.5)	CuCl (0.25)	Et_3N (5)	25	4 h	77.3	22.7	0	0	0	0	0	0
23	DMF (0.5)	CuCl (0.5)	DIPEA (5)	25	7 h	34.8	45.1	7.5	6.1	0	0	0	0
24	DMF (0.5)	$Cu(OAc)_2$ (0.5)		25	20 h	0	59	21.3	6.7	0	0	0	0
25	DMF (0.5)	Cu (0.5)		25	48 h	66.7	7.5	1	0	0	0	2	21
26	DMF (0.5)	Cu (0.5)	Ultrasound	25	4 h	0	45.8	29.9	16.1	6.4	1.8	0	0

[a] asc.ac.—Ascorbic acid.

entry 26). The influence of solvents such as acetonitrile, acetone, EtOH and THF on the reaction course was also tested. All these solvents were inferior to DMF. The results of these experiments are summarised in Table 1, entries 12–15.

In conclusion, we have confirmed that the cyclisation of azidobenzoate **1** using click chemistry results in the production of a mixture of macrocycles. This mixture was successfully analysed. The reaction was very sensitive to the reaction conditions, and it was demonstrated that it was possible to modify the ratio of the macrocycles by varying the reaction conditions. In addition, the results showed that various copper salts have significantly different effects on the reaction. This study also revealed the distinct properties of copper(I) iodide relative to other copper halides, and the important role of the addition of various tertiary amines was demonstrated. The studied reaction provides an economic method for the preparation of larger quantities of the studied macrocycles**.** Column chromatography is necessary for the preparation of macrocycles **3**, **4** or higher. Chromatographic separation of macrocycles was described recently.[6]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.076.

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7. A solution of propargyl 2-azidobenzoate (**1**) (25 mg, 0.1205 mmol) in DMF (0.15 mL) was added to a solution of the catalyst or to a solution of the catalyst and the co-catalyst in DMF (0.35 mL), and the reaction mixture was stirred at a given temperature for the appropriate amount of time. Samples (1 drop) were diluted with H_2O (1 mL) and extracted with EtOAc (0.5 mL). Samples were taken after 15 min and 30 min and then in 1 h intervals. The reaction performed at temperature −15 °C was conducted in a refrigerator evaporator, and a chest freezer was used for the reaction performed at −25 °C. These reactions were not stirred but were shaken during sampling. Long-duration reactions were sampled only during working hours. The reaction details are summarised in Table 1.
8. LC/MS analyses were performed with a Thermo Exactive instrument (Thermo Scientific, USA). The chromatographic apparatus consisted of an Accela 1250 LC pump, an autosampler and a column thermostat. The separation was performed on a Luna C18, 3 μm, 50 × 2 mm i.d. column (Phenomenex, USA) using binary gradient elution. The mobile phase comprising acetonitrile and water with 0.1% formic acid was mixed from 30 to 50% of acetonitrile over a period of 8 min, followed by isocratic elution up to 12 min stop time. A 5 min equilibration was performed before the next injection. The flow rate was kept at 300 μL/min, and the column temperature was 30 °C. Samples were prepared as follows: 200 μL of EtOAc solution was evaporated using a vacuum at laboratory temperature (5 min), the residue was dissolved in 10 mL of a 9:1 mixture of acetonitrile and water (1 min sonication), and then 200 μL of this solution and 800 μL of a 3:7 mixture of acetonitrile and water were added and mixed as a final dilution before the injection of 10 μL. An exactive high-resolution mass spectrometer based on an orbitrap mass analyser was used with Atmospheric Pressure Chemical Ionisation (APCI). The spectrometer was tuned to obtain the maximum response for *m*/*z* 90–1300. The source parameters were set to the following values: APCI temperature 400 °C, spray voltage +3.5 kV, transfer capillary temperature 330 °C and sheath gas/aux gas (nitrogen) flow rates 25/10. The separated compounds were observed by recording the TIC (total ion current)/time signal, and the area % was calculated for quantification. The HRMS spectra of the target peaks allowed the determination of their elemental compositions due to the high intensities of their protonated molecules. The identification of the respective structures was performed, and the differences between the experimental and calculated values were less than 1 ppm.