Improved Method for the Preparation of Macrocyclic Diamides

Daniel T. Gryko,[a] Dorota Gryko,[a] Janusz Jurczak[a,b]*

[a] Institute of Organic Chemistry Polish Academy of Sciences01-224 Warsaw, Poland
Fax +48 (22) 6326681; E-mail: jurczak@ichf.edu.pl
[b] Department of Chemistry University of Warsaw 02-093 Warsaw, Poland

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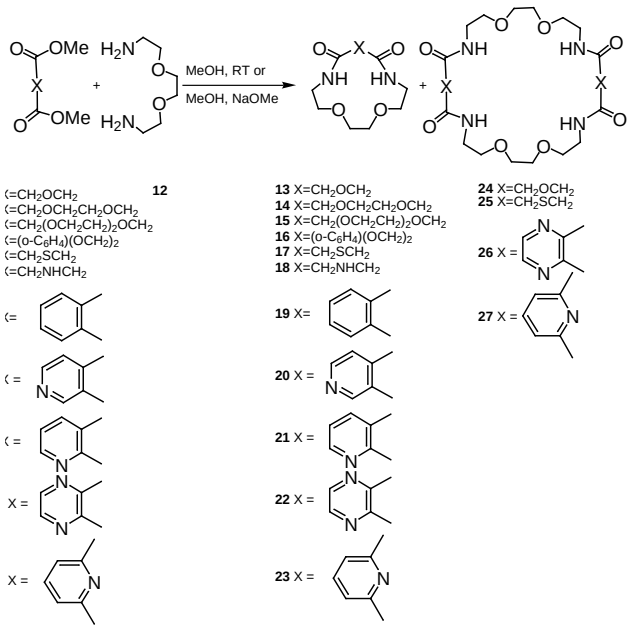
Abstract: Sodium methoxide was found to be an effective catalyst in the reaction of diesters with diamines leading to macrocyclic diamides. The time of reaction was shortened by about 20 times as compared with previous results (to several hours usually). Additionally, yields of desired products were improved by about 2-8 times.

Key words: amides, aminations, crown compounds, macrocycles, sodium.

There is continued interest in the preparation of diazacoronands because they can be used as macrocyclic molecular receptors as well as valuable intermediates for the synthesis of cryptands and related compounds.[1] The methods for the formation of diazacoronands have been extensively reviewed.[2] Among the currently available methods, the high-dilution technique,[3] the route based on the template effect,[4] and the high-pressure approach,[5] are frequently used. At the end of the eighties, Morphy et al.[6] reported that, consistent with the earlier findings of Tabushi,[7] no high-dilution technique was required for the reaction of malonates with α,ω-diamines to form macrocyclic diamides. These observations prompted us to apply a similar approach to the synthesis of a broad range of diazacoronands. We initially found[8] that α,ω-diamino aliphatic ethers reacted under ambient conditions with dimethyl α,ω-dicarboxylates, to afford the macrocyclic diamides (Scheme). These diamides can be readily transformed into the corresponding diamines using, for example, $BH_3 \times Me_2S$.[3,8b] Optimal reaction conditions proposed by us are as follows: methanol as a solvent, room temperature, 7 days, concentration ~0.1 M (throughout this paper referred to 'standard conditions'). These conditions or similar ones were recently used by us[9] and others[10] for preparing several types of macrocyclic amides. The main advantage of our method is that no additional external cyclization factor (as high-dilution approach or template effect) is required to obtain satisfactory results. The disadvantage of this approach is long reaction time. During these studies we observed that the addition of weak organic bases shortened the reaction time slightly. We also noted that *tert*-butyl esters (unreactive under standard conditions) react with diamines in the presence of DBU.[9c,e] These facts prompted us to seek a general catalyst to accelerate the reaction of diesters with diamines. Based on the mechanism of the amidation reaction,[11] and on results of studies on the reaction of monoesters with monoamines,[12] we assumed that methoxides or hydroxides added in sufficient amount to the mixture of diester and diamine in methanol would accelerate the reaction. To confirm this, we began our current study using the previously studied esters **1–4**.[8b] Our initial experiments were directed at exploring the influence of the amount of NaOMe on the time of reaction of diesters with diamines (based on the 100% conversion of diesters). After a few experiments, we established 100 mol% of NaOMe as a reasonable amount to shorten the reaction time significantly. The reaction of diesters **1**–**4** with diamine **12** in MeOH in the presence of 100 mol% of NaOMe afforded macrocyclic diamides **13**–**16** and tetraamide **24** after only 7-8 hours as compared with 140-160 h without NaOMe (Scheme, Table 1). That means that reaction time was shortened by about 20 times. The reactions were carried out by adding the diamine and diester to preformed sodium methoxide in methanol at 5 ºC.[13]



It is noteworthy that the yield is the same (**14**–**16**) or higher (**13**) than under standard neutral conditions. At the same time, the ratio of diamide **13**: tetraamide **24** is improved from 7:1 to 24:1. The significantly higher yield of diamide **13** in the presence of NaOMe can be explained by base-accelerated intramolecular reaction of the intermediate compound possessing one free ester group and one free amino group. It is possible, that the increase of yields

Table 1. Results of reactions of esters **1**-**11** with diamine **12** under various conditions.

	MeOH, RT				MeOH, MeONa, RT			
Ester	Conversion of diester (%)	Yield of diamide (%)		Yield of tetraamide (%)	Conversion of diester (%)	Yield of diamide (%)		Yield of tetraamide (%)
1	91[a]	**13**	50[8b]	**24** 8	100[d]	**13**	73	**24** 3
2	100[a]	**14**	68[8b]	0	100[d]	**14**	70	0
3	99[a]	**15**	50[8b]	0	100[d]	**15**	52	0
4	98[a]	**16**	73[8b]	0	100[d]	**16**	74	0
5	83[a]	**17**	26	**25** 2	100[c]	**17**	57	**25** 10
6	57[a]	**18**	40	0	100[c]	**18**	75	0
7	4[b]	**19**	2	0	69[c]	**19**	16	0
8	14[b]	**20**	4	0	88[c]	**20**	36	0
9	17[b]	**21**	8	0	100[c]	**21**	62	0
10	81[c]	**22**	38	**26** 5	100[d]	**22**	48	**26** 7
11	97[a]	**23**	83[9d]	**27** 6	100[d]	**23**	84	**27** 3

[a] Reaction time 7 days. [b] Reaction time 4 weeks. [c] Reaction time 2 weeks. [d] Reaction time 8 hours. [e] Reaction time 48 hours.

observed by us are associated with the template effect due to the Na^+ ion. In order to check this, we next examined the transformation of diesters **1** and **3** into diamides **13** and **15** in the presence of bases possessing various cations (LiOMe, NaOMe, NaOH, KOMe, CsOH) (Table 2).

Comparison of the results shows that there is no template effect in these reactions. There is no significant difference in the yield of diamide **13** as well as in the yield of diamide **15** (differing only in the size of ring) depending on what cation is present in the reaction mixture. It is very important to use anhydrous methanolates instead of metal hydroxides. When we used NaOH or CsOH the yield of diamides **13** and **15** decreased by about 20%. We attribute the lower yields to nucleophilic attack of OH^-, which leads to partial hydrolysis of the starting esters.

Table 2. Results of reactions of esters **1** and **3** with diamine **12** in the presence of various catalysts, performed in methanol.

Base, time [h]	Yield of **8** (%)	Yield of **14** (%)	Yield of **10** (%)
- 168	50[8b]	8	50[8b]
MeOLi, 12	73	3	51
MeONa, 12	73	3	52
MeOK, 12	70	3	51
NaOH, 12	47	2	28
CsOH, 12	49	2	26

Prompted by these results, we decided to use esters **5** and **6** possessing sulfur and nitrogen atoms with the α,ω-diamine. Without any catalyst, we observed 100% conversion for these cases in 3-4 weeks. In the presence of 100 mol% of NaOMe, the reaction time was shortened to 48 hours, and the yields of diamides **17** and **18** were respectively 2.2 and 1.9 times higher then without catalyst (Scheme, Table 1).

We next examined esters **7–11** which were derived from the aromatic acids. The yields of diamides **19–22** under standard conditions are, with exemption of **22**, very low even after prolongation of reaction time (Scheme, Table 1). All the yields, as well as conversions of starting esters, are strongly dependent on the positions of the carbonyl groups in relation to nitrogens in the heteroring. Experiments performed in the presence of 100 mol% of NaOMe afforded the desired diamides **19–22** after 2 weeks in much better yields. In all cases, it is possible to use larger amounts of sodium methoxide in order to shorten the reaction time. For example, using 1000 mol% of NaOMe allowed the reaction time of **10** with **12** to be shortened to 2 days. It is noteworthy that in the case of diester **10**, significant amounts of the tetraamide **26** were produced (5% and 7% depending on the conditions).

In the case of dimethyl pyridine-2,6-dicarboxylate **11** (studied by us previously[9d]), the reaction time was also shortened to 7-8 hours (Scheme, Table 1).

In conclusion, we have developed a simple catalyst system for the reaction of diesters with diamines leading to macrocyclic diamides. We strongly believe that significant shortening the reaction times as well as increasing the yields makes this method very competitive in relation to the classic high-dilution approach. This method should find its place in the growing arsenal of modern synthetic methods for constructing macrocyclic compounds.

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(13) **General procedure**: Sodium (230 mg, 10 mmol) was added to 8anhydrous methanol (100 mL). Then the mixture was cooled to 5 °C and the α,ω-diamine (10 mmol) and dimethyl dicarboxylate (10 mmol) were added. This mixture was left at ambient temperature over a period of 8 hours (or longer). Then the solvent was evaporated together with a small amount of silica gel and the residue was chromatographed on silica gel using 0-10% mixtures of methanol in CH_2Cl_2 as eluants. All new compounds afforded correct elemental analysis and spectroscopic data. For example:**1-Thia-7,9-dioxa-4,13-diazacyclopentadecane-3,14-dione (17)**: mp 126-128°C; IR (KBr): ν = 3297, 2911, 1666, 1647, 1554, 1440, 1312, 1180, 1138, 1074, 1022; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.33 (s, 4H), 3.4-3.5 (m, 4H), 3.6-3.7 (m, 8H), 7.13 (bs, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 36.8, 39.3, 68.9, 69.5, 167.8; MS (EI) m/z (%):44 (38.7), 70 (26.2), 85 (73.2), 86 (53.5), 87 (20.6), 88 (23.6), 130 (17.3), 157 (21.7), 173 (18.5), 216 (22.6), 219 (20.8), 262 (100) [M^+]; HREIMS: calcd $C_{10}H_{18}O_4N_2S$ [M^+] 262.0987; found 262.0992; $C_{10}H_{18}O_4N_2S$ (262): calcd C 45.79, H 6.92, N 10.68, S 12.22; found C 45.83, H 7.08, N 10.73, S 12.24. **1,16-Dithia-7,10,22,25-tetraoxa-4,13,19,28-tetraazatriacontane-3,14,18,29-tetraone (25)**: mp 222-224°C; IR (KBr): ν = 3264, 3062, 2878, 1645, 1558, 1142, 1104; ^{1}H NMR (200 MHz, CF_3COOD): δ = 3.7-3.9 (m, 16H), 3.9-4.0 (m, 16H); ^{13}C NMR (50 MHz, CF_3COOD): δ = 37.8, 42.8, 70.6, 71.8, 177.2; MS (LSIMS) m/z (%) :525 (39) [MH^+], 547 (4) [MNa^+]; HRLSIMS: calcd $C_{20}H_{37}O_8N_4S$ [$M+H^+$] 525.2053; found 525.2085; $C_{20}H_{36}O_8N_4S_2$ (524): calcd C 45.79, H 6.92, N 10.68, S 12.22; found C 46.04, H 7.20, N 10.47, S 12.31.

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