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Daniel T. Gryko[a]; Dorota Gryko[a]; Janusz Jurczak[ab]
[a] Institute of Organic Chemistry Polish Academy of Sciences, Warsaw [b] Department of Chemistry, University of Warsaw, Warsaw, Poland

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An Influence of Structure of Ester on Results of Its Macrocyclization Reaction with α,ω-Diamine

DANIEL T. GRYKO[a], DOROTA GRYKO[a] and JANUSZ JURCZAK[ab*]

[a]*Institute of Organic Chemistry Polish Academy of Sciences, 01–224 Warsaw and* [b]*Department of Chemistry University of Warsaw, 02–093 Warsaw, Poland*

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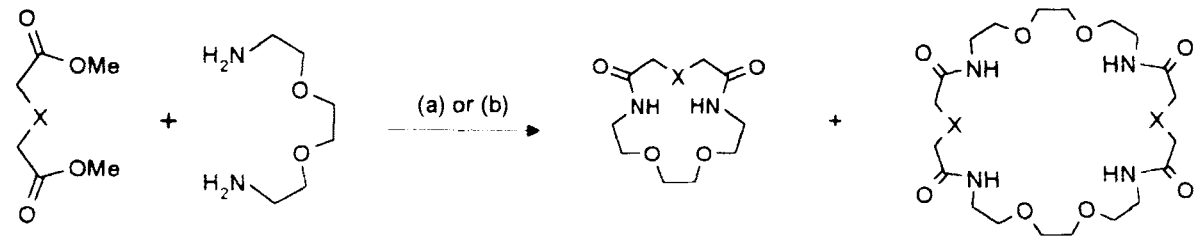
Sodium methoxide was found to be an excellent catalyst in the reaction of diesters with diamines leading to macrocyclic diamides. Time of reaction was shortened to several hours (in the case of reactive esters) or to several days (in the case of less reactive esters). The template effect of Na^+ ion was excluded. It was also proposed that the electron density on the carbonyl group in various esters was responsible for different results of amidation reactions. Decrease in electron density increases the reactivity of the carbonyl group. For esters **1–5**, the inductive effect of the heteroatom at the α position to the carbonyl group influences reactivity mostly.

Keywords: Amides, hydrogen bonds, macrocycles, sodium methoxide

There is a continuous interest in the preparation of diazacoronands which find important applications as macrocyclic molecular receptors as well as valuable intermediates for the synthesis of cryptands and related compounds [1,2]. The methods of formation of diazacoronands have been extensively reviewed [3–5]. Among these methods, the high-dilution technique [6], the route based on the template effect [7], and the high-pressure approach [8] are frequently used as the most versatile procedures. At the end of the eighties Morphy *et al.* [9] have reported that, consistent with the earlier findings of Tabushi [10,11], no high-dilution technique was required for the reaction of malonates with α,ω-diamines to form the macrocyclic diamides. These facts prompted us to apply a similar approach to the synthesis of broad range diazacoronands. At the beginning of the nineties we found [12–14] that α,ω-diamino aliphatic ethers reacted under ambient conditions with dimethyl α,ω-dicarboxylates, to afford the macrocyclic diamides which can be readily transformed into the corresponding diamines. Optimal reaction conditions proposed by us are as follows: methanol as a solvent, room temperature, seven days, concentration ~0.1 M. These conditions or similar ones were recently used for preparing several types of macrocyclic amides [15]. During the detailed studies on this method we observed that the addition of weak organic bases shortened the reaction time slightly.

Based on mechanism of the amidation reaction [16] and on results of studies on the reaction monoesters with monoamines [17], we found that addition of 100 mol% NaOMe caused huge acceleration of reactions shown in Scheme 1. Sodium methoxide, which is the strongest base

* Author for correspondence.



1 X=O
2 X=S
3 X=NH
4 X=CH_2
5 X=CH_2OCH_2

6

7 X=O
8 X=S
9 X=NH
10 X=CH_2
11 X=CH_2OCH_2

12 X=O
13 X=S

SCHEME 1 (a) MeOH, RT, 168 hours; (b) MeOH, NaOMe, RT, 12 hours

existing in methanol, causes as shown in Table I that:

- esters **1**, **2** and **3**, which gave good yields of macrocyclic amides after seven days, react now for 7–10 h in conversion of 100%, with high yield of product;
- esters **4** and **5**, which do not react under standard conditions, react now for one-three weeks giving macrocyclic products in moderate yields.

It was possible, that the increase of yields, observed by us, is assiociated with the template effect of Na^+ ion. In order to check this possibility we carried out reactions of ester **1** with diamine **6**, using bases possessing various cations (LiOMe, NaOMe, NaOH, KOMe, CsOH) (Table II). Results show clearly that we do not observe any template effect. The yield of diamides is the same when we use either LiOMe or NaOMe or KOMe. However, it is very important to use anhydrous methoxides instead of metal hydroxides. When we use NaOH or CsOH the yield of diamide **7** decreases by about 20%. This is probably connected with nucleophilic attack of OH^-, which leads to partial hydrolysis of the starting ester.

TABLE I Reactions of esters **1–5** with diamine **6** under various conditions

Ester	*MeOH, RT*			*MeOH, MeONa, RT*		
	Conversion of diester (%)	*Yield of diamide (%)*	*Yield of tetramide (%)*	*Conversion of diester (%)*	*Yield of diamide (%)*	*Yield of tetramide (%)*
1	91[a]	53	8	100[c]	73	3
2	83[a]	26	2	100[d]	57	10
3	57[a]	40	0	100[d]	75	0
4	0[b]	0	0	100[a]	20	0
5	0[b]	0	0	100[a]	20	0

Reaction time: 7 days[a], 4 weeks[b], 12 hours[c], 48 hours[d].

TABLE II Reactions of esters **1** with diamine **6** in the presence of various catalysts[a]

Catalyst		*MeOLi*	*MeONa*	*MeOK*	*NaOH*	*CsOH*
Time	*7 days*	*12 h*	*12 h*	*12 h*	*12 h*	*12 h*
Yield of diamide **7** (%)	53	73	73	70	47	49
Yield of tertraamide **2** (%)	8	3	3	3	2	2

a. All reactions were performed in methanol.

Keeping above-mentioned facts in mind, we assumed that the electron densities on the carbonyl group in various esters are responsible for different results of the bisamidation reactions. In order to check this hypothesis, we analysed results of the reaction of esters **1–5** with diamine **6** under standard conditions (Scheme 1, Table I). We expected that the lower electronegativity of heteroatoms in esters **1–4** would cause decrease in their conversion as well as yields of macrocyclic amides. Results shown in Table I confirm this expectation. We obtained diamides **7–9** and tetramides **12** and **13** in moderate to good yield. For ester **1**, containing the most electronegative oxygen atom, conversion is the highest. Replacement of the oxygen atom with sulphur or nitrogen (esters **2** and **3**) causes considerable decrease of conversion of ester and yield of macrocyclic product. We did not observe any macrocyclic products derived from ester **4**. It is obvious that many factors can influence the electron density of the carbonyl group. For aliphatic esters, the main one is the inductive effect derived from heteroatom at the α position to the carbonyl group. Our results show that the carbonyl group is strongly activated by a heteroatom at the α position. Remaining doubts relating to influence of the inductive effect on the reactivity of the carbonyl group in this reaction are explained by making experiment with ester **5**. This ester possess the ethereal oxygen atom at the β position to the carbonyl group, so the inductive effect is very small in this case. Consequently, we did not observe any conversion what confirms our hypothesis.

Heteroatom at the α position is necessary in order to the conversion would be high. Nevertheless, it is not enough to obtain macrocyclic products in satisfactory yield. Dimethyl tartrate possess oxygen atom from the hydroxyl group at the α position to the carbonyl group. Therefore conversion is high, but the yield of macrocyclic products is low.

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