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A convenient and efficient route for the synthesis of amidecrownophanes via 1:1 macrocyclization of di(acid chloride) with diamine derivatives

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Abstract—Four amidecrownophanes **3a**–**d**, including three new compounds **3a**, **3c** and **3d**, were readily prepared through amidation of dicarbonyl dichloride with diamine derivatives without using high-dilution or template conditions and then the tandem Claisen rearrangement. At the macrocyclization step the intramolecular hydrogen bonding of the intermediate might play an important role to give high yields of 1:1 macrocycles.

Over the past few decades, macrocyclic compounds have become important synthetic targets due to their wide applications in host–guest supramolecular chemistry.[1] Crownophane-type macrocycles, which have the ability of H-bonding, are particularly attractive for their excellent property to recognize inorganic and organic cations, anions and neutral substrates strongly and selectively. They can also be used as platforms for the design of supramolecular systems (e.g., rotaxanes and catenanes).[2] In our previous work, we synthesized many crownophanes with hydroxyl groups as H-bond donors via tandem Claisen rearrangement (TCR), which have been proved to serve not only as anion sensors but also as precursors for constructing rotaxanes.[3]

So, the precise design and efficient synthesis of various crownophanes has continued to be a very important issue in the area of supramolecular chemistry. Although up to now, many kinds of crownophanes were prepared, development of a mild and effective synthetic route to this type of macrocycles still remains an attractive and challenging subject for synthetic chemists because the existing methods have to employ some special reaction conditions, such as high-dilution,[2e,3,4a,b] and template control,[4c] to compensate for the extra large enthalpic and entropic disadvantageous features during the course of macrocyclization.[5]

Herein, we report an unusually convenient and efficient route for the preparation of crownophanes with two amide groups and two hydroxyl groups, generally called 'amidecrownophanes', via the direct amidation of di(acid chloride) with diamine derivatives and then TCR reaction (Scheme 1). The key ring-forming step is very attractive because it can be achieved under mild and normal conditions instead of using special high-dilution or template control to give the 1:1 macrocyclic products in good yields.

In fact, our original aim was to synthesize acyclic oligoamide compounds by reacting di(acid chloride) with excess (about 10 equimolar amounts) diamine derivatives in THF at room temperature. Under this condition it may be expected to obtain mainly acyclic products with amino end groups instead of macrocycles when adding di(acid chloride) dropwise to the solution containing such dense diamine derivatives. Nevertheless, an unexpected result was obtained, that is, the main products were 1:1 macrocycles. When we used 1,6-hexanediamine as a reactant to react with di(acid chloride) under the conditions that 0.5 mmol of **1** in 10 mL THF was added dropwise into 5 mmol of 1,6-hexanediamine also in 10 mL THF solution, and the solution was stirred overnight at room temperature, macrocyclic compound **2a** was surprisingly obtained in 81% yield. To confirm this unusual result, we tried the reactions using other diamine derivatives as a reactant, such as 1,2-bis(2-aminoethoxy)ethane and 1,12-dodecamethylenediamine

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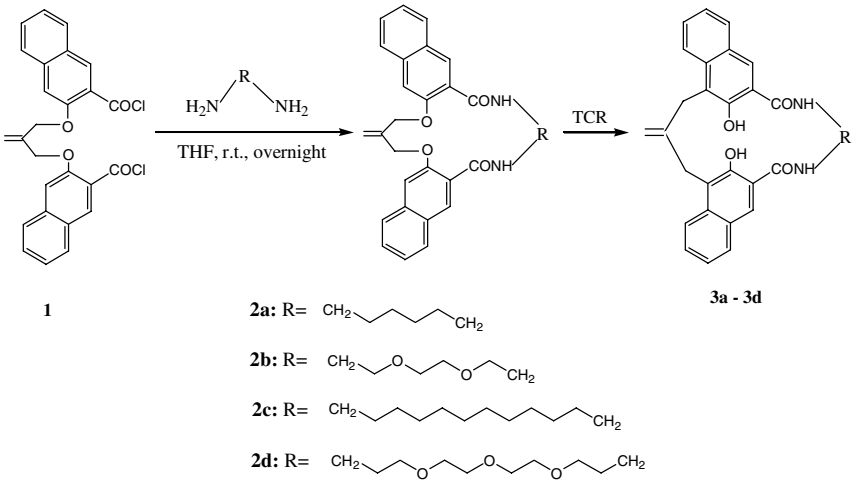


Scheme 1. Synthesis of amidecrownophanes via macrocyclization and tandem Claisen rearrangement.

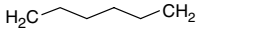
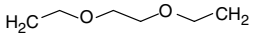
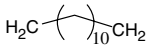
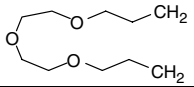
which have a longer molecular chain than 1,6-hexanediamine, and it was found that the corresponding macrocyclic compounds **2b** and **2c** were readily obtained in 70% and 38% yield, respectively.

It should be noted that 1:1 macrocyclic formation predominantly proceeded, even under such high ratio of diamines toward di(acid chloride) **1**. Thus, this process provided a very convenient and efficient route to give macrocycles having various ring sizes in good yields without high-dilution conditions or template control.

To study this unusual reaction in more detail, we carried out the experiments under different conditions. We investigated the influence of the ratio between di(acid chloride) **1** and diamine derivatives on the formation of macrocycles. Analyzing the two reactants and the molecular structure of macrocyclic products, we can know clearly that it is a 1:1 amidation reaction. Accordingly, we reacted equimolar amounts of di(acid chloride) and four different diamine derivatives in THF at room temperature in order to improve the yields;[6] the selected substrates of diamines and the yields of macrocycles obtained are summarized in Table 1.[7] As expected, the yields of the corresponding macrocycles were all improved compared with the former conditions; especially for the reaction of di(acid chloride) with 1,12-dodecamethylenediamine, the yield of macrocycle **2c** was increased dramatically from 38% to 60%. From this result, we could conclude that the 1:1 ratio is optimum in the macrocyclization of di(acid chloride) with diamine derivatives.

Additionally, we carried out the experiment by changing the addition order of these two reactants, that is, the reaction proceeded under the conditions that diamine derivatives were added dropwise into the THF solution containing di(acid chloride) **1**. It was interestingly found that changing the addition order of these two reactants had little effect on the formation of macrocycles because the corresponding macrocyclic products were obtained in almost the same yields as in the former process (e.g., **2a**: 86%→83%; **2b**:[8] 74%→71%). This result indicates that the predominant formation of macrocycles might proceed through a key intermediate as shown in Figure 1. It is assumed that, as soon as the first amide is formed in the reaction of **1** with diamines, the second amino group quickly and intramolecularly approaches another acid chloride group by the formation of multiple hydrogen bondings to give rise to the predominant formation of 1:1 macrocycles.[9] In contrast, if the amidation proceeds simultaneously, it could also be imagined that other intermolecular reactions, in which polymers or oligomers will be formed, must occur to decrease

Table 1. Yields of the macrocyclization[a] and rearrangement

Entry	–R–	Macrocyclization		Conditions of rearrangement	Rearrangement	
		Product	Yield (%)		Product	Yield (%)
1a		**2a**	86	Without solvent 170 °C, 1 h	**3a**	81
1b		**2b**	74	Without solvent 150 °C, 1 h	**3b**	81
1c		**2c**	60	Without solvent 170 °C, 1 h	**3c**	83
1d		**2d**	52	Without solvent 150 °C, 1 h	**3d**	82

[a] Reaction conditions: see Ref. 6.

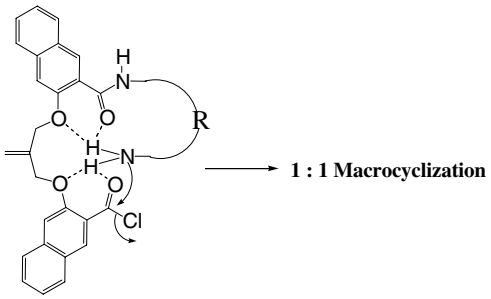


Figure 1. A postulated conformational key intermediate for 1:1 macrocyclization.

the yield of macrocycles drastically when diamine derivatives were added dropwise to the solution of extremely high molar ratio of di(acid chloride) toward diamine.

Furthermore, from the data of Table 1, it is noted that the yield of macrocyclic compounds **2** decreases correspondingly with the increase of the molecular chain length of diamine derivatives. This fact may imply that the second intramolecular attack of the end amine group to another acid chloride strongly depends on the chain length of the diamine part after the first amidation of di(acid chloride) with one of the amine groups of diamine derivatives occurred. Further evidence supporting our assumption is now under investigation.

In order to confirm the limitation of this reaction, we tried to react 1,6-hexamethylenediamine with suberoyl chloride under the same conditions. The corresponding 16-membered macrocycle was not obtained at all, but the oligomerization occurred. On the other hand, the reaction of 1,3-bis(3-methoxycarbonylnaphthyl-2-oxy)-propane with 1,6-hexamethylenediamine under the same conditions gave 1:1 macrocycle in 25% yield.[10] This result means the isobutenyl group might play an important role to favorably effect 1:1 macrocyclization even under no high-dilution condition. The isobutenyl group seems to be entropically advantageous for intramolecular macrocyclization compared to a trimethylene chain. These results might support the proposed mechanism as shown in Figure 1.

The tandem Claisen rearrangement was carried out smoothly by heating **2a–d** without a solvent in vacuum only for 1 h and the corresponding amidecrownophanes were obtained in high yields, respectively, as shown in Table 1.

In summary, we have reported an uncommonly convenient and effective method to synthesize amidecrownophanes having two hydroxyl groups in good yields. Further development of this strategy and potential application of the new amidecrownophanes are ongoing.

References and notes

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6. General procedure for the synthesis of macrocyclic compound **2**: A solution of diamine derivatives (1 mmol) containing Et_3N (200 mg, 2 mmol) in 20 mL tetrahydrofuran (THF) was prepared in a flask and was cooled by ice-water bath, then isobutenyl binaphthyl di(acid chloride) **1** (0.465 g, 1 mmol), also in 20 mL THF, was added dropwise to the solution over a period of about 20 min and stirring was continued overnight at room temperature. THF was evaporated off under reduced pressure and water was added into the residue to give a solid. The solid was filtered off, washed several times with water and dried. Purification was performed by column chromatography with mixed AcOEt and $CHCl_3$ as the eluent. Polyether compounds **2** were achieved as the main products in good yields.
Compound **2a**: white solid; yield 86%; mp 141–142 °C; ^{1}H NMR (500 MHz, $CDCl_3$), $\delta = 1.53$ (m, 4H, –CH_2–CH_2–), 1.70 (m, 4H, –CH_2–CH_2–), 3.57 (m, 4H, CONH–CH_2–), 4.95 (s, 4H, –O–CH_2–), 5.68 (s, 2H, CH_2=C–), 7.27 (s, 2H, naphthyl), 7.43 (dd, $J = 7$ Hz, 2H, naphthyl), 7.54 (dd, $J = 7.5$ Hz, 2H, naphthyl), 7.73 (d, $J = 8.5$ Hz, 2H, naphthyl), 7.88 (br, 2H, NH), 7.92 (d, $J = 8$ Hz, 2H, naphthyl), 8.75 (s, 2H, naphthyl) ppm; ESI-MS (cationic mode), 531.8 (M + Na); elemental analysis, found (calcd for $C_{32}H_{32}N_2O_4$), C, 75.27 (75.57); H, 6.29 (6.34); N, 5.44 (5.51).
Compound **2b**: white solid; yield 74%; ^{1}H NMR (500 MHz, $CDCl_3$), $\delta = 3.63$–3.75 (m, 12H, –CH_2–), 4.99 (s, 4H, –O–CH_2–), 5.57 (s, 2H, CH_2=C–), 7.22 (s, 2H,

naphthyl), 7.40 (dd, $J = 7$ Hz, 2H, naphthyl), 7.52 (dd, $J = 7.5$ Hz, 2H, naphthyl), 7.72 (d, $J = 8$ Hz, 2H, naphthyl), 7.90 (d, $J = 8$ Hz, 2H, naphthyl), 8.41 (br, 2H, NH), 8.76 (s, 2H, naphthyl) ppm.

Compound **2c**: white solid; yield 60%; mp 144–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$), $\delta = 1.31$–1.36 (m, 12H, –CH_2–), 1.41–1.45 (m, 4H, –CH_2–), 1.59–1.65 (m, 4H, –CH_2–), 3.51–3.55 (m, 4H, –CH_2–), 4.98 (s, 4H, –O–CH_2–), 5.60 (s, 2H, CH_2=C–), 7.16 (s, 2H, naphthyl), 7.41 (dd, $J = 3$ Hz, 2H, naphthyl), 7.43 (dd, $J = 3.5$, 2H, naphthyl), 7.46 (d, $J = 4.5$ Hz, 2H, naphthyl), 7.83 (br, 2H, NH), 7.91 (d, $J = 8$ Hz, 2H, naphthyl), 8.75 (s, 2H, naphthyl) ppm; ESI-MS (cationic mode), 615.9 (M + Na); elemental analysis, found (calcd for $C_{38}H_{44}N_2O_4 \cdot 1/3H_2O$), C, 76.31 (76.22); H, 7.47 (7.51); N, 4.62 (4.68).

Compound **2d**: white solid; yield 52%; mp 135.5–136.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$), $\delta = 1.84$–1.89 (m, 4H, –CH_2–), 3.41–3.43 (m, 4H, –O–CH_2–), 3.45–3.47 (m, 4H, –O–CH_2–), 3.50–3.53 (m, 4H, –O–CH_2–), 3.55–3.61 (m, 4H, –CONH–CH_2–), 4.99 (s, 4H, –O–CH_2–), 5.61 (s, 2H, CH_2=C–), 7.20 (s, 2H, naphthyl), 7.40 (dd, $J = 7$ Hz, 2H, naphthyl), 7.47 (dd, $J = 7.5$ Hz, 2H, naphthyl), 7.58 (d, $J = 8$ Hz, 2H, naphthyl), 7.88 (d, $J = 8$ Hz, 2H, naphthyl), 8.09 (br, 2H, NH), 8.61 (s, 2H, naphthyl) ppm; ESI-MS (cationic mode), 635.9 (M+Na); Elemental analysis, found (calcd for $C_{36}H_{40}N_2O_7 \cdot 1/2H_2O$), C, 69.68 (69.55); H, 6.72 (6.65); N, 4.29 (4.51).

7. The characterization of new amidecrownophans **3a**, **3c** and **3d**:

   Compound **3a**: yellow solid; yield 81%; mp 99–100 °C; ^{1}H NMR (500 MHz, $CDCl_3$), $\delta = 1.39$–1.92 (m, 8H, –CH_2–CH_2–), 3.41–3.44 (m, 4H, –CONH–CH_2–), 3.60–3.66 (m, 4H, Ar–CH_2–), 3.93 (s, 2H, CH_2=C–), 6.97 (s, 2H, naphthyl), 7.30–7.38 (m, 2H, naphthyl), 7.48–7.59 (m, 2H, naphthyl), 7.72 (br, 2H, NH–), 7.80–7.98 (m, 2H, naphthyl), 8.50 (s, 2H, naphthyl), 10.63 (s, 2H, –OH) ppm; ESI-MS (cationic mode), 531.7 (M+Na); elemental analysis, found (calcd for $C_{32}H_{32}N_2O_4 \cdot 1/3CHCl_3$), C, 75.27 (75.57); H, 6.29 (6.34); N, 5.44 (5.51).

   Compound **3c**: yellow solid; yield 83%; mp 99.5–100.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$), $\delta = 1.11$–1.88 (m, 20H, –CH_2–CH_2–), 3.17–3.24 (m, 4H, –CONH–CH_2–), 3.54–3.73 (m, 4H, Ar–CH_2–), 4.05–4.13 (m, 2H, CH_2=C–), 7.11 (s, 2H, naphthyl), 7.28–7.43 (m, 2H, naphthyl), 7.55–7.58 (m, 2H, naphthyl), 7.75 (br, 2H, NH–), 7.95–7.96 (m, 2H, naphthyl), 8.60 (s, 2H, naphthyl), 12.39 (s, 2H, –OH) ppm; ESI-MS (cationic mode), 615.8 (M+Na); elemental analysis, found (calcd for $C_{38}H_{44}N_2O_4$), C, 76.90 (77.00); H, 7.48 (7.48); N, 4.67 (4.73).

   Compound **3d**: yellow solid; yield 82%; mp 90–91 °C; ^{1}H NMR (500 MHz, $CDCl_3$), $\delta = 1.90$–1.95 (m, 4H, –CH_2–CH_2–), 3.55–3.60 (m, 4H, –O–CH_2–), 3.67–3.72 (m, 8H, –O–CH_2–), 3.78–3.81 (m, 4H, –CONH–CH_2–), 3.96 (s, 4H, Ar–CH_2–), 5.28 (s, 2H, CH_2=C–), 7.11–7.12 (m, 2H, naphthyl), 7.29–7.32 (m, 2H, naphthyl), 7.43 (br, 2H, NH–), 7.47–7.53 (m, 2H, naphthyl), 7.55 (s, 2H, naphthyl), 7.96 (d, $J = 8.5$ Hz, 2H, naphthyl), 11.06 (s, 2H, –OH) ppm; ESI-MS (cationic mode), 635.8 (M+Na);. elemental analysis, found (calcd for $C_{36}H_{40}N_2O_7 \cdot 1/2H_2O$), C, 69.77 (69.55); H, 6.76 (6.65); N, 4.31 (4.51).

8. The preparation of **2b** and **3b** has already been reported under the high dilution method (yields: **2b** 32%; **3b** 82%) Yoshida, H.; Saigo, K.; Hiratani, K. *Chem. Lett.* **2000**, 116–117.

9. It was reported macrocycle that 2:2 macrocyclization occurred in the reaction of di(acid chloride) with *p*-phenylene diamine under the normal conditions. In that case, it was also presumed that hydrogen bonding in the noncyclic intermediate might play an important role to form 2:2 macrocycle Numata, M.; Hiratani, K.; Nagawa, Y.; Houjou, H.; Masubuchi, S.; Akabori, S. *New J. Chem.* **2002**, *26*, 503–507.

10. Under the same conditions as in the case of the formation of **2a**–**d**, the reaction of 1,3-bis(3-chlorocarbonylnaphthyl-2-oxy)propane with 1,6-hexamethylenediamine gave 1:1 macrocycle in 25% yield: white solid; mp 263–264 °C; ^{1}H NMR (500 MHz, DMSO-d_6), $\delta = 1.47$ (m, 4H, –CH_2–CH_2–), 1.60 (m, 4H, –CH_2–CH_2–), 3.48 (m, 4H, CONH–CH_2–), 4.36 (m, 4H, –O–CH_2–), 7.28 (s, 2H, naphthyl), 7.40 (dd, $J = 5$ Hz, 2H, naphthyl), 7.53 (dd, $J = 5$ Hz, 2H, naphthyl), 7.86 (d, $J = 8$ Hz, 2H, naphthyl), 7.94 (d, $J = 8$ Hz, 2H, naphthyl), 8.17 (br, 2H, NH), 8.18 (s, 2H, naphthyl) ppm.