Beneficial Effect of Mukaiyama Reagent on Macrobislactamization Reactions

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Abstract: An expeditious two-step procedure was developed to accede to new tetraamide macrocycles. The key step of this diversity-oriented procedure is a highly efficient Mukaiyama salt promoted macrobislactamization. Preliminary mechanistic investigations are also reported.

Key words: tetraamide macrocycles, Mukaiyama reagent, macrobislactamization

Tetraamide macrocycles have not been thoroughly exploited in host–guest chemistry,[1] although they present interesting electronic (aromaticity), structural (rigidity) and coordination (convergent H-bond donating N–H amide groups) properties.[2] This low solicitation may originate from the difficulties encountered to synthetically accede to them, despite their apparent structural simplicity. We were particularly surprised not to find any general route for the synthesis of tetraaromatic tetraamide macrocycles (Figure 1), with the exception of a brief communication reporting on the positive effect of molecular crowding on macrocyclization.[3]

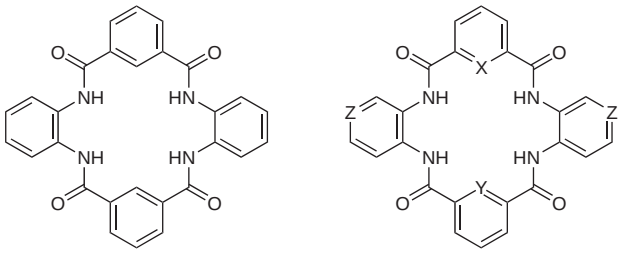

Figure 1 Structures of targeted tetraamide macrocycles

In this context, and stimulated by recent reports on structurally related compounds,[2,4,5] we decided to investigate the possibilities to synthesize tetraaromatic tetraamide macrocycles. To this purpose, we focused our attention on macrocycles ranging form previously reported tetrabenzotetraamide to unknown tetrapyridotetraamide macrocycles (**1** and **5**, respectively, Figure 1). Our initial plan was devoted to establish short, convenient and scalable syntheses. In that sense, the possibility of performing challenging, and unreported, macrobislactamization step between readily accessible dianilines and diacid moieties was investigated.

We first focused our attention on the cyclization precursors, namely the trisbenzo-, dibenzopyrido- and trispyridodiamine **6**, **7** and **8**, respectively (Scheme 1). The synthesis of **7** was reported by Sessler et al. as a three-step procedure (80% yield),[5] based on reaction between activated dipicolinic acid and mono-protected phenylene diamine. We developed an alternative three-step pathway to obtain **7** and **8**, based on classical *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDCI)-promoted coupling reaction between dipicolinic acid and mono-protected diamine (*ortho*-phenylene diamine and 3,4-diaminopyridine, respectively); the subsequent acidic deprotection afforded **7** and **8** with good overall chemical yield (56% and 87% respectively, Scheme 1). More interestingly, we observed that phenylene diamine can be coupled directly without any particular reagent protection or activation, which could be a major advantage to scale up the process. The access to **6** and **7** was thus readily shortened to a one-step procedure, with good yields (81% and 77% respectively, Scheme 1).[6]

Our first idea was to benefit from the widely used pyridine pre-organization via internal H-bond network (schematically represented as dotted line in Scheme 2).[2] First macrobislactamization reactions were thus attempted with **7** and **8**, following the classical Ruggli's procedure,[7] i.e. high dilution conditions and slow addition of activated diacids. To our surprise, we were unable to isolate cyclized products upon reaction between **7** and a broad panel of diacids. More astonishingly, only the starting material was recovered when the reactions were performed with **8**, despite considerable efforts in varying the conditions. This lack of reactivity seemed general since extensive trials always resulted in the same conclusions. The reactivity of **7** and **8** was then further investigated. Under more reactive conditions as compared to macrocyclization ones (i.e. 3 equiv of more reactive AcCl) we obtained only moderate amount of bisacetyl-**7** and unmodified **8**. These results were explained by a complete deactivation of NH_2 moiety by the intracyclic nitrogen in *para* position in **8**, besides a steric hindrance which is invoked to explain the low reactivity of **7**.

To circumvent these reactivity problems, we turned our attention to Mukaiyama's reagent (*N*-methyl-2-chloropyridinium iodide, Scheme 2). This salt has been widely

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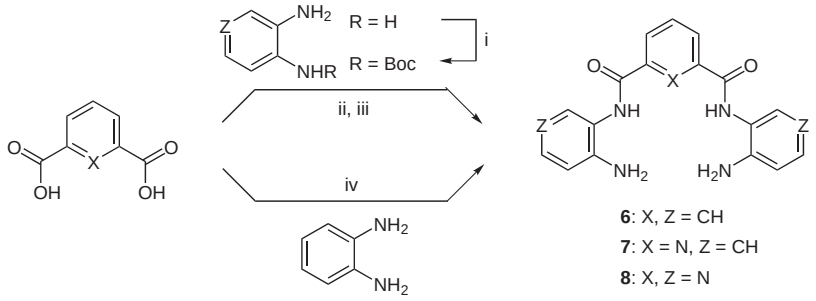


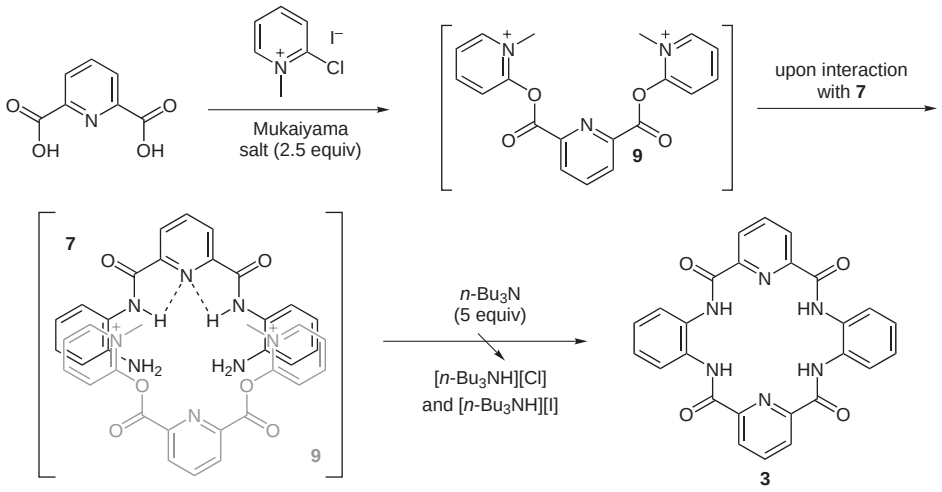
Scheme 1 Synthesis of **6**, **7** and **8**. *Reagents and conditions*: (i) $(Boc)_2O$, THF, 77% (Z = CH), 100% (Z = N); (ii) EDCI, 1-hydroxyazabenzotriazole (HOAt), DMF, 100% (Z = CH), 99% (Z = N); (iii) TFA, CH_2Cl_2, 100% (**7**; X = N, Z = CH), 88% (**8**; Z, X = N); (iv) EDCI, HOAt, DMF, 81% (**6**; X = CH) and 77% (**7**; X = N). See ref.[6] for detailed experimental conditions.

used to perform lactamization reactions,[8] bislactamization[9] and very efficient macrolactamization,[10] but never for achieving concomitant macrobislactamization. This reaction is generally assumed to involve an intermediate resulting from *ipso*-substitution of highly reactive chlorine atom by carboxylic function. It was thus appealing to postulate that this intermediate could exist as bispyridinium **9** (Scheme 2). Interestingly, this postulated intermediate exhibits a remarkable shape complementarity with **7** (and/or **8**). This could highly favor the formation of an organized transition state, based on the perfect π-stacking overlap between **7** and **9** (schematically represented in Scheme 2).

To investigate this hypothesis, we tried to obtain macrocycles **2** and **3** following the classically reported lactamization protocol: a diluted dichloromethane solution of dipicolinic or isophthalic acid and **7** was heated at reflux overnight in presence of 2.5 equivalents of pyridinium salt and five equivalents of tri-*n*-butylamine (to scavenge released HI and HCl). The reaction mixture was then cooled, and the final product precipitated upon addition of diethyl ether. Macrocycles **2** and **3** were isolated in excellent yields (73% and 71%, respectively) and purity.[6] In contrast, the reaction proceeded in only moderate yield (29%) when conducted with **7** and the monoacid isobutanoic acid (**C**, Table 1). Additionally, very low yields (<2%) were obtained upon reaction between **7** and the geometrically non-optimized *ortho*- or *para*-disubstituted benzenedioic acid [phthalic (**D**) and terephthalic (**E**) acid, respectively]. Furthermore, we observed that, when the substrate offers suitable geometrical dispositions (two acid functions in *meta* position), additional organizations (e.g. internal H-bonds) are not required. Indeed, as depicted in Table 1, the synthesis of macrocycle **2** was of comparable efficiency when conducted with the internally H-bonded **7** (upon reaction with diacid **A**, 73%) or with **6** (upon reaction with diacid **B**, 82%). The efficiency of the process was evidenced by the high yielding synthesis of **1**, from **6** and **A** which are not prone to internal organization (85%, Table 1).

Altogether these observations strongly support the formation of the highly ordered transition state, which in turn greatly enhances the overall reactivity of the system. However, we have so far not been able to isolate the reaction intermediate **9** in order to fully confirm our hypothesis.

Results are summarized in Table 1; only trisbenzo- and dibenzopyridodiamine **6** and **7** reacted under these conditions, for reactivity reasons presented previously. However, results obtained with **6** and **7** are quite impressive since macrocycles **1**, **2** and **3** were readily obtained in the yields



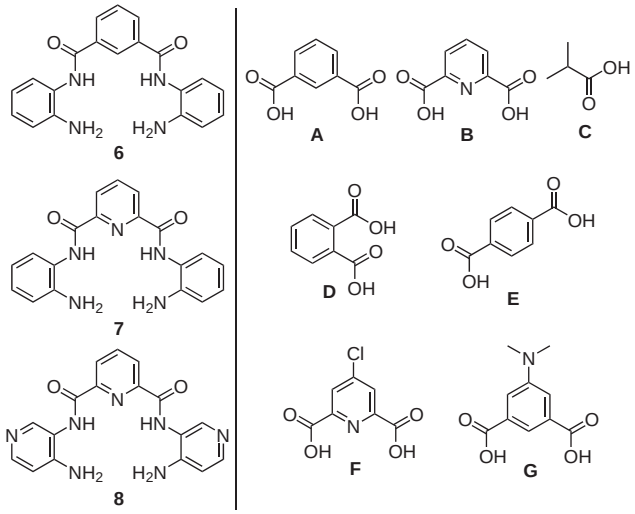
Scheme 2 Mechanistic proposals for macrobislactamization reaction between dipicolinic acid and **7**.

of 70–85%. This reaction appears somewhat sensitive to electronic factors. Indeed, while the introduction of electron-donating moiety (NMe_2, $\sigma_p^+ = -1.70$)[11] can be included without disrupting the macrobislactamization efficiency (**7** + **G**, 72%), introducing an electron-withdrawing one (Cl, $\sigma_p^+ = 0.11$)[11] alters significantly this efficiency (**7** + **F**, 48%). This moderate yield probably results from an electronically driven reduced probability of forming bispyridinium intermediate, which in turn disfavors the cyclization step.

Table 1 Chemical Yields of Macrobislactamization Step between Various Diamines (**6**–**8**) and Acids (**A**–**G**)[a,b]

	A	B	C	D	E	F	G
6	(**1**) 85%	(**2**) 82%	n.a.[c]	n.a.[c]	n.a.[c]	n.a.[c]	n.a.[c]
7	(**2**) 73%	(**3**) 71%	29%	>2%	>2%	48%	72%
8	(**4**) 0%	(**5**) 0%	0%	n.a.[c]	n.a.[c]	n.a.[c]	n.a.[c]

[a] See below for structural description of **6**–**8** and **A**–**G**.
[b] See ref.[6] for typical procedure description.
[c] n.a. = not attempted.



In conclusion, we have developed a straightforward procedure to the unexplored family of tetraaromatic tetraamide macrocycles. Access to these molecules has been shortened to a two-step procedure, via the development of a very efficient Mukaiyama salt promoted macrobislactamization step. The generality of the reaction has been proven by the structural diversity of the macrocycles obtained which opens perspectives for wider synthetic employments. First insights toward mechanistic elucidation are also proposed. Preliminary complexation studies are currently underway and the results will be reported in due time.

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(6) **Two-step Synthesis of Tetraaromatic Tetraamide Macrocycles; General Procedure**:
Step 1: **One-Step Synthesis of Diamine 6 and 7**
ortho-Phenylene diamine (1.85 mmol, 2.0 equiv), EDCI (1.94 mmol, 2.1 equiv) and HOAt (0.37 mmol, 0.4 equiv) were successively added to a solution of diacid derivative (isophthalic or dipicolinic acid; 0.92 mmol, 1.0 equiv) in DMF (50 mL) under an inert atmosphere. After the addition, the reaction mixture was allowed to stir at r.t. for 16 h. The mixture was concentrated under reduced pressure to a crude oil that was purified by flash column chromatography (silica gel, CH_2Cl_2–5% MeOH) to afford the expected diamine (**6** or **7**) as a pale yellow powder, with chemical yields given in the text. Compound **6**: R_f 0.6 (CH_2Cl_2–10% MeOH); mp 198 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.77 (s, 2 H), 8.59 (s, 1 H), 8.15 (br d, *J* = 7.8 Hz, 2 H), 7.66 (t, *J* = 7.7 Hz, 1 H), 7.20 (d, *J* = 7.8 Hz, 2 H), 6.99 (td, *J* = 8.2 Hz, *J*′ = 1.3 Hz, 2 H), 6.80 (dd, *J* = 8.1 Hz, *J*′ = 1.2 Hz, 2 H), 6.62 (td, *J* = 8.2 Hz, *J*′ = 1.3 Hz, 2 H), 4.94 (br s, 4 H). ^{13}C NMR (75.3 MHz, DMSO-d_6): δ = 165.0, 143.6, 135.2, 131.0, 128.8, 127.7, 127.2, 127.1, 123.5, 116.7, 116.6. Compound **7**: R_f 0.17 (CH_2Cl_2–5% MeOH); mp 240 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.70 (s, 2 H), 8.18–8.35 (m, 3 H), 7.16 (dd, *J* = 7.8 Hz, *J*′ = 1.2 Hz, 2 H), 7.03 (td, *J* = 8.1 Hz, *J*′ = 1.5 Hz, 2 H), 6.81 (dd, *J* = 8.1 Hz, *J*′ = 1.2 Hz, 2 H), 6.63 (td, *J* = 7.5 Hz, *J*′ = 1.2 Hz, 2 H), 5.00 (br s, 4 H). ^{13}C NMR (75.3 MHz, DMSO-d_6): δ = 162.5, 149.3, 144.5, 140.0, 128.0, 127.7, 125.2, 122.7, 116.7, 116.4.
Step 2: **Macrobislactamization Reaction for the Synthesis of 1**, **2 and 3**
Mukaiyama salt (2-chloromethylpyridinium iodide; 0.75 mmol, 2.5 equiv), tri-*n*-butylamine (1.5 mmol, 5.0 equiv) and the diamine derivative (**6** or **7**, 0.3 mmol, 1.0 equiv) were successively added to a solution of diacid derivative (isophthalic or dipicolinic acid, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) under an inert atmosphere. The reaction mixture was stirred at reflux temperature for 16 h. After cooling to r.t., Et_2O (200 mL) was added providing a white precipitate that was collected by filtration. The corresponding tetraaromatic tetraamide macrocycles (**1**, **2** or **3**) were obtained as a white powder, with chemical yields given in Table 1. Compound **1**: mp 310 °C. IR (KBr): 3240 (NH), 1648 (CO), 1603 (NH), 1303 (CN), 755 (CH) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.18 (br s, 4 H), 9.16 (d, *J* = 5.4 Hz, 2 H), 8.50–8.63 (m, 3 H), 8.38 (d, *J* = 8.1 Hz,

2 H), 8.20 (d, *J* = 8.4 Hz, 1 H), 7.52–7.70 (m, 4 H), 7.22–7.40 (m, 4 H). EI–MS: *m*/*z* (%) = 477 (67) [M + H^+]. Compound **2**: mp 304 °C. IR (KBr): 3474 (NH), 3245 (CH), 1685 (CO), 1591 (NH), 1307 (CN), 749 (CH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 10.94 (s, 2 H), 10.17 (s, 2 H), 8.24 (br t, 3 H), 8.00–8.12 (m, 1 H), 7.68 (br d, 2 H), 7.52 (m, 4 H), 7.21 (m, 4 H), 6.75 (m, 1 H). EI–MS: *m*/*z* (%) = 479 (100) [M + H^+], 496 (8) [M + NH_4^+]. Compound **3**: mp 196 °C. IR (KBr): 3423 (NH), 3247 (CH), 1677 (CO), 1600 (NH), 1308 (CN), 754 (CH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 11.00 (s, 4 H), 8.40 (d, *J* = 8.0 Hz, 4 H), 8.30 (t, *J* = 7.7 Hz, 2 H), 7.82–7.86 (m, 4 H), 7.37–7.41 (m, 4 H). EI–MS: *m*/*z* (%) = 479 (30) [M + H^+], 496 (28) [M + NH_4^+].

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