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Cite this: RSC Advances, 2013, 3, 691 Received 7th November 2012, Accepted 8th November 2012 Rapid and efficient solvent-free synthesis of cyclophanes based on bipyridinium under mechanical ball milling[†]

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We reported here the first rapid and solvent-free templatedirected preparation of cyclophanes based on bipyridinium, which was achieved using mechanical ball milling. The method affords a new strategy for construction of diverse substituted CBPQT·4PF₆, which greatly shortens the reaction period, rendering this methodology practical in the field of supermolecular chemistry.

The cyclophanes based on the general structure represented by cyclobis(paraquat-p-phenylene) (CBPQT⁴⁺) comprise one of the most important molecules in contemporary supermolecular chemistry.1 Their photophysical, photochemical and electrochemical properties have recently been reported on pseudorotaxanes, cantenanes and rotaxanes, respectively.2 Hünig and co-workers first reported the synthesis of the cyclophanes based on two 4,4'bipyridinium moieties linked via different o- or m-xylene bridges.³ In 1988, Stoddart and co-workers first synthesized CBPQT·4PF₆ with a yield of only 12% using MeCN as solvent.⁴ Thereafter, with the rapid development of supermolecular chemistry, considerable attention was given to the synthesis of these supermolecular compounds using molecular templates.⁵ Several templates, such 1,4-bis[2-(2-hydroxyethoxy)ethoxy],⁶ as 1,4-bis[2-2(2-hydroxythoxy)],7 1,5-bis[2-(2-hydroxyethoxy)ethoxy]naphth-alene8 and 1,5-bis[2-(2-methoxy)ethoxy]naphthalene9 have been developed to increase the yields of CBPQT·4PF₆. In addition to employing templates, it was also discovered that the efficiency of the reactions could be improved by changing the reaction solvent from MeCN to DMF and carrying out the reaction at ultra-high pressure (12-15 kbar).9 Higher yields were obtained under different reaction conditions, which are not strictly comparable and the ultra-high pressure conditions present potential safety risks. Purification of the CBPQT·4PF₆ product requires the removal of the molecular template from the reaction mixture using liquid–liquid extraction. Recently, Stoddart's group found that a pH-sensitive derivative of 1,5-diaminonaphthalene could displace the template and eliminate the need for the lengthy liquid–liquid extraction step.¹⁰

Using the traditional methods, a series of novel CBPQT·4PF₆ with different substituents were reported.¹¹ However, CBPQT·4PF₆ containing electron-withdrawing groups are seldom reported or obtained in yields greater than 5–35%.^{11,12} Previously, our work focused on synthesizing diverse substituted CBPQT·4PF₆¹² and studying the interactions between these cyclophanes and phenyl ether derivatives.¹³ In light of our recent success in this area, we attempted to synthesize novel cyclophanes **4a** and **4b** *via* the traditional methodology (see ESI[†]) as depicted in Schemes 1 and 2. Nevertheless, the two preparative methods require a long term (in practice, more than three weeks) and consume large quantities of solvent, respectively. To avoid these disadvantages, there has been an urgent need to develop a new rapid, convenient and environmentally friendly method to produce cyclophane compounds.

In recent years, solvent-free organic reactions have drawn considerable attention due to their environmentally benign protocols, short reaction time, favorable yields, convenient means of product purification and occasionally-enhanced selectivity.¹⁴ From a practical point of view, the mechanical ball milling technique has been considered as a powerful tool in promoting various organic transformations under solvent-free conditions,



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including organocatalysis,¹⁵ oxidative aminations of aldehydes,¹⁶ dehydrogenation of γ -terpinene,¹⁷ Mn(OAc)₃-mediated cycloadditions,¹⁸ metal-mediated cross-couplings¹⁹ and the synthesis of aryl chlorides and bromides.²⁰ For example, Chiu and co-workers have synthesized rotaxanes by ball milling with a high isolation yield (81%),²¹ more efficient than solution-based reactions.²²

To the best of our knowledge, the use of mechanical milling techniques to prepare CBPQT·4PF₆ has not been described in the literature. In view of the limitation of the existing methods, we report here a practical methodology for preparing different substituted CBPQT·4PF₆ under ball milling conditions.

Initially, we chose the reaction of 3a with 1,4-bis(bromomethyl)benzene 2c as the model reaction. Typically, a mixture of 2c (0.2 mmol), 3a (0.2 mmol) and 5 or 6 (0.6 mmol) was directly milled vigorously at room temperature (Table 1). The vibration frequency was set at the highest (30 Hz). After 30 min, only trace products were observed without any additives (Table 1, entry 1). Prolonging the reaction time to 60 min resulted in no improvement in yield. Normally the kinetic energy generated by the action of the milling balls is transferred to the reaction mixture, which drives the reaction. Then, we tried adding various additives such as NaCl to the reaction system. After all, we did find that the yield could be improved slightly from 4-7% by adding SiO₂, Al₂O₃ or NaCl to dilute the concentration of the reaction (Table 1, entries 8-10), but yield was still poor. In general, we found that reaction of half-cyclophane 3a with 2c in the absence of a template yielded poor self-assembly of the desired product 4a with many oligomer and linear polymer byproducts. Employing a molecular template could force the half-cyclophane compounds to interact with the templates and the bipyridinium units resulting in a cis conformation.⁶ This would be beneficial to the cyclization step.

Subsequently, we conducted a series of pre-assembled experiments. At first, **3a** was dissolved in anhydrous MeCN (5 mL), and then various templates **5** or **6** and additives were added to the solution. Next, the mixture was refrigerated at -10 °C for 60 min, followed by the removal of the solvent *in vacuo* at room temperature. Last, the solid mixture was transferred to the ball milling vessel and milled with **2c** for 30 min at rt. As shown in Table 1, template **6** proved to be more effective than **5** for the cyclization reaction step. Perhaps because of their structures, the naphthalene ring should be more polarizable and could place more electrons of its π surface inside the CBPQT·4PF₆ than the latter.²³ In addition, the yield using SiO₂ and Al₂O₃ was higher than that using NaCl. This maybe was due mainly to the function

Table 1 Optimization of reaction conditions for the synthesis of 4a^a



^{*a*} The reaction mixture of 1,4-bis(bromomethyl)benzene **2c** (1.0 equiv), **3a** (1.0 equiv), template **6** (3.0 equiv) and additives (1.0 equiv) was milled at 30 Hz for 30 min. ^{*b*} Isolated yields obtained by silica gel column chromatography. ^{*c*} **3a** and template **6** were assembled before the reaction. ^{*d*} **3a**, template **6** and **2c** were milled directly.

of SiO₂ and Al₂O₃ in that they acted as dispersing agents and also provided effective molecular adsorption, thereby maintaining the configuration of the self-assembly. By contrast, NaCl was merely a reaction diluent and offered poor molecular adsorption. The preassembled solvent-free cyclization reaction in SiO₂ using template **6** resulted in the best yield of **4a** in 22% (Table 1, entry 10), which was similar to the reaction performed in an organic solvent (24%).

Having defined the optimal reaction, we proceeded to explore the scope and generality of this transformation using various bipyridinium precursors **3** and dibromides **2**. The results of these experiments are listed in Table 2. As shown, a series of cyclophane products **4** were achieved in 15–25% in a very short period compared with the conventional method. Moreover, the relatively low yield of **4b** (Table 2, entries 2, 3) might be due to the steric hindrance of the substitution on the cyclophane. As a result, the yields of cyclophanes containing a nitro group and fluorine atoms, were higher than the yields using cyclophanes. Compared to the traditional methods, our method sharply reduces the reaction period from more than 2 weeks to 1.5 h, giving similar yields.

The identification of new compounds was fully confirmed by their MALDI-TOF-MS, ¹H NMR and ¹³C NMR. The structures of **4a** and **4b** were further confirmed by X-ray crystallography. As presented in Fig. 1, rigid rectangular box-like conformations with two paraquat units forming the longer sides, with the two opposite phenylene residues forming the shorter sides, were adopted. The twist angles relating the mean planes of the two pyridinium rings Table 2 The comparative synthesis of different substituted CBPQT·4PF₆



Entry	R	R'	Product	Condition A ^a		Condition B^b	
				Time (min)	Yield (%) ^c	Time (day)	Yield (%) ^c
1	$ 2a$ $\frac{NO_2}{2a}$	-<	4a	30	20	21	23
2	-\	CH ₂ OH	4b	30	17	60	19
3	2b	-\		30	15	90	16
4	-\	-\	4 c	30	19	12	23 ⁸
5	$-\underbrace{\sim}^{F}_{2d}$	-\	4d	30	25	14	28 ^{12a}

^{*a*} The reaction mixture of **2** (1.0 equiv), **3** (1.0 equiv), template **6** (3.0 equiv) and silica gel (1.0 equiv) was milled at 30 Hz for 30 min. In addition, **3** and template **6** were assembled before the reaction. ^{*b*} The reaction mixture **2** (1.0 equiv), **3** (1.0 equiv), template **6** (3.0 equiv) and a catalytic amount of NaI was dissolved in anhydrous MeCN. ^{*c*} Isolated yields obtained by chromatography on silica gel.

in the bipyridinium units of **4a** and **4b** change remarkably in comparison to the distortion of different substituted CBPQT·4PF₆, which have been reported.^{4,12a} Furthermore, the interactions between **4a** or **4b** and various π -electron-rich donors will be well studied in our further investigations.

In summary, a novel rapid and efficient protocol for the synthesis of various substituted cyclobis(paraquat-*p*-phenylene) tetracations in acceptable yields using a mechanical milling process is reported. Particularly noteworthy is the fact that this solvent-free procedure makes the synthesis of cyclophane compounds more efficient, economical and ecologically-friendly, rendering this methodology useful in the field of supermolecular chemistry.



Fig. 1 An ORTEP diagram of compounds 4a and 4b

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