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Synthesis of [2]- and [3]rotaxanes through Sonogashira coupling

Jean-Benoît Giguère, Dominic Thibeault, Francis Cronier, Jean-Sébastien Marois, Michèle Auger, Jean-François Morin *

Département de chimie and Centre de Recherche sur les Matériaux Avancés, 1045 Ave de la Médecine, Pavillon Alexandre-Vachon, Université Laval, Québec (Qc), Canada G1V 0A6

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ABSTRACT

The synthesis of new [2]- and [3]rotaxanes through Sonogashira coupling has been accomplished in the aim to built oligo(phenyleneethynylene) (OPE) encircled by crown ethers. Optimization of the Sonogashira coupling for the formation of the [2]rotaxane (capping reaction) is presented and the best method has been applied for the synthesis of the longer [3]rotaxane.

The preparation of synthetic molecular machines mimicking functions of those found in nature is one of the biggest challenges in nanoscience.[1] In the past decades, chemists exploited a large variety of organic reactions to construct simple and complex nanoarchitectures able to perform tasks upon chemical[2] or physical[3] stimulation. Rotaxane is undoubtedly the most used supramolecular assembly for the preparation of functional nanomachines. Rotaxane consists of a dumbbell-shaped rod encircled by a mechanically interlocked macrocycle than can move along the rod in a translational fashion upon stimulation.[1a,e,4] Over the past ten years, several synthetic methods have been developed to enable the preparation of different types of rotaxane and to allow the introduction of functional groups. This is especially true for rotaxanes having an ammonium-crown ether conjugate and particular attention has been given to the development of new methodologies to end-cap these rotaxanes. These include, among others, the formation of urethane with isocyanate,[5] ester from anhydride derivatives,[6]disulfide,[7] triazole via click chemistry,[8] and alkene by ruthenium-catalyzed metathesis[9] and Wittig reaction.[10] However, to the best of our knowledge, an end-capping reaction using palladium-catalyzed C–C cross-coupling has never been reported to end-cap rotaxane. The rather harsh reaction conditions, especially the presence of strong base, polar solvents and the high temperature needed to achieve cross-coupling reaction are incompatible with the formation of rotaxanes based on ammonium-crown ether conjugate that rely solely on hydrogen bonds. Thus, it is a real challenge to prepare such rotaxane using the standard cross-coupling methods.

As a part of our research program aiming at preparing rotaxane-based supramolecular rotors working in the solid state, we decided to investigate the feasibility of Sonogashira coupling to prepare [2]- and [3]rotaxanes. Sonogashira coupling has been chosen among others since it allows the synthesis of phenylacetylene derivatives, which are well-known building blocks for the preparation of molecular machines.[11] Few examples of oligo(phenyleneethynylene) (OPE)-based rotaxane have been reported so far,[12] but none of them was prepared using crown ether macrocycle. Thus, we report herein the first synthetic efforts to prepare [2]- and [3]rotaxanes (Fig. 1) based on ammonium-crown ether conjugate through Sonogashira coupling. Because there is no report of such reaction for rotaxane formation and end-capping, we investigated different reaction conditions for the capping of a [2]rotaxane to optimize the yield of reaction. The best conditions have been applied for the synthesis of the [3]rotaxane.

The rod of the rotaxane bearing the ammonium group was synthesized in four steps as depicted in Scheme 1. First, 4-hydroxybenzaldehyde was alkylated with propargyl bromide in acetone to give compound **4** in quantitative yield. Then, a condensation reaction between compounds **5**[13] and **3** in refluxing toluene in a Dean–Stark apparatus followed by a reduction of the imine to a secondary amine using $LiAlH_4$ provided **6** in 92% yield (two steps). The amine was finally protonated using HCl followed by an ion exchange with NH_4PF_6 to give the ammonium-containing rod **7** in 68% yield.

Using compound **7** and 3,5-dimethyliodobenzene, several attempts to form a [2]rotaxane were performed and the results are summarized in Table 1.

As a starting point, we have studied the reaction under standard Sonogashira coupling conditions using $PdCl_2(PPh_3)_2$ as the catalyst and NEt_3 as the base (entry 1). Because rotaxane formation is possible only in aprotic solvents that are unable to interact through hydrogen bonding with the ammonium, we used CH_3CN rather than THF or DMF. Unfortunately, the yield obtained when 2.2 equiv of NEt_3 was used is rather low (12%). Interestingly, by decreasing the amount of triethylamine to 1.1 equiv, the reaction yield doubled to reach 25% (entry 2). The presence of NEt_3 is likely to be responsible for the poor yield since it is known to efficiently deprotonate the ammonium group once the rotaxane is formed.[13] Thus, we decided to use a modified method developed by Verkade

* Corresponding author.
E-mail address: jean-francois.morin@chm.ulaval.ca (J.-F. Morin).

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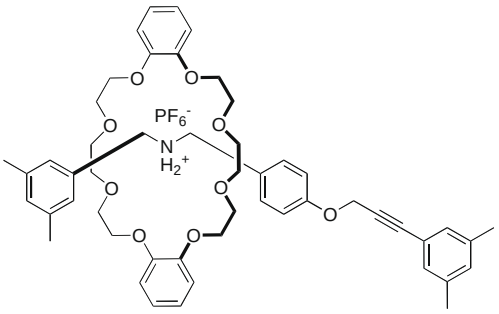
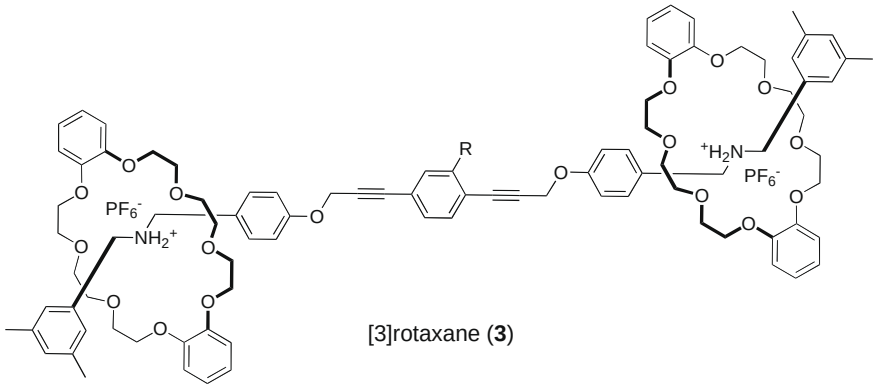
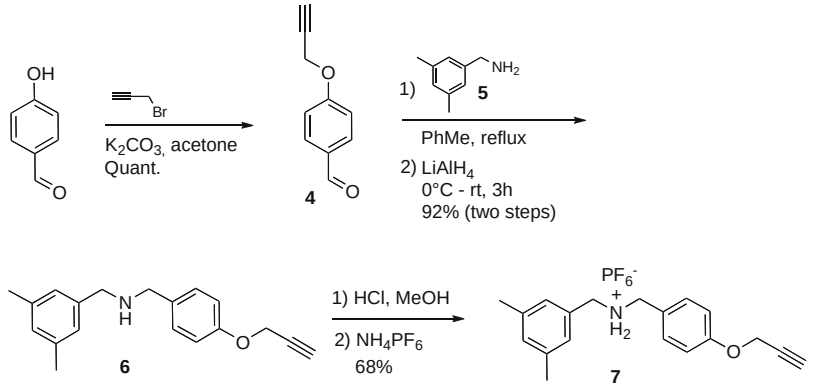


[2]rotaxane (**1**)



[3]rotaxane (**3**)

Figure 1. Structure of the [2]- and [3]rotaxanes obtained by Sonogashira couplig.

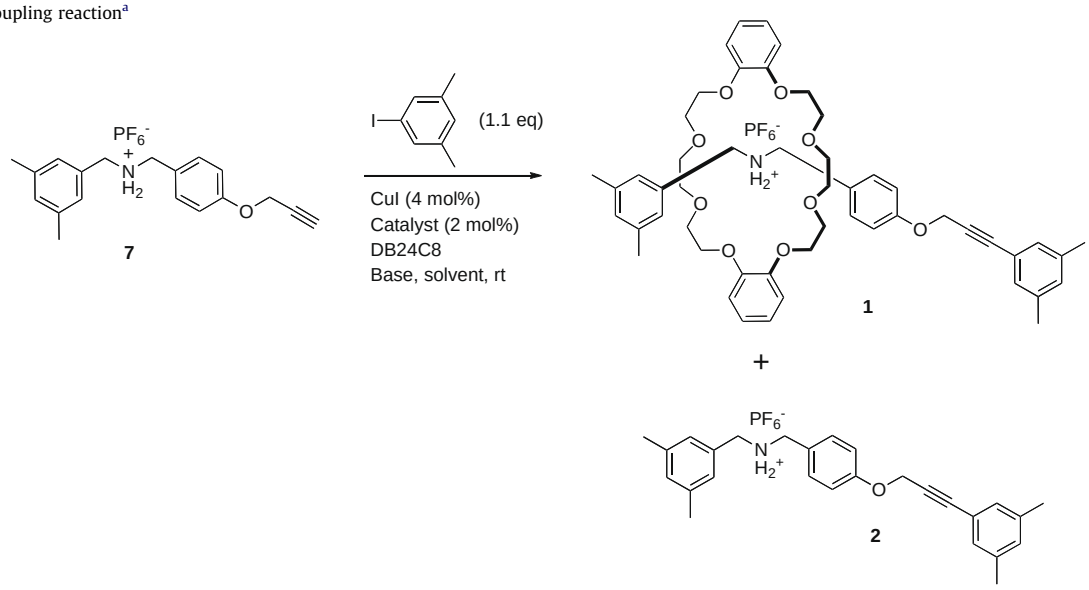


Scheme 1. Synthetic route for the synthesis of the ammonium-containing rod.

et al. using tetrabutylammonium acetate (Bu_4NOAc) as a weak base for Sonogashira coupling (entries 3–6).[14] It should be noted that Me_4NOAc has been used instead of Bu_4NOAc since the methyl derivative is much easier to remove in the workup than the butyl one. The use of acetate as the base provided lower reaction yields than NEt_3 (entries 3 and 4), even when other palladium catalysts were used (entries 5 and 6). Different bases were thus tried (entries 7–11), but only trace amounts of the desired product was obtained. Therefore, we decided to investigate a more hindered base having a structural similarity to NEt_3, namely *N*-isopropyl-*N*-methyl-*tert*-butylamine (*i*PM*t*BA). The reaction with 2.0 equiv of base provided the desired rotaxane in 18% yield (entry 12). The yield of the reaction can further be increased (26%) by decreasing the amount of base down to 1.08 equiv (entry 16). Adding more DB24C8 to the reaction mixture to drive the reaction (entry 13), adding the base dropwise to the reaction mixture (entry 17) or starting the reaction at 0 °C to drive the formation of the pseudo[2]rotaxane in solution (entry 18) do not increase the reaction yield. The low yields obtained for the capping reaction of a rotaxane by Sonogashira coupling can be explained in different ways. First, the steric hindrance near the alkyne can be responsible in part for the low yield. In fact, steric hindrance due to the crown ether macrocycle is known to be responsible for low yields in many types of rotaxane transition metal-mediated capping reactions.[9] Many attempts to cap a [2]rotaxane using Sonogashira coupling with an ammonium derivative having an alkyne directly attached to the phenyl group were all unsuccessful. This suggests that the proximity of the alkyne to the macrocycle is an important factor for the success of this reaction. Moreover, the choice of solvent and base to optimize the reaction is rather limited since rotaxanes can be formed only in specific conditions of pH (no strong bases), temperature (no heat), and polarity (no hydrogen bond).

Interestingly, the yields obtained for compound **2** (end-capped rod) are higher than those obtained for compound **1** meaning that

Table 1
Optimization of coupling reaction[a]



Entry	Catalyst	Base	Equiv of base	**1** (%)	**2**[g] (%)
1	$PdCl_2(PPh_3)_2$	NEt_3	2.2	12	
2	$PdCl_2(PPh_3)_2$	NEt_3	1.1	25	49
3	$PdCl_2(PPh_3)_2$	Me_4NOAc	2.0	10	
4	$PdCl_2(PPh_3)_2$	Me_4NOAc	1.5	16	34
5	$Pd(OAc)_2$	Me_4NOAc	1.5	0	
6	$PdCl_2$(dppf)	Me_4NOAc	1.5	0	
7	$PdCl_2(PPh_3)_2$	Imidazole	1.5	0	
8	$PdCl_2(PPh_3)_2$	DBU	2.0	0	60
9	$PdCl_2(PPh_3)_2$	DABCO	2.0	<5	51
10	$PdCl_2(PPh_3)_2$	2,6-lutidine	1.1	<5	
11	$PdCl_2(PPh_3)_2$	Me_2NAr[e]	1.1	0	
12	$PdCl_2(PPh_3)_2$	*i*PM*t*BA[f]	2.0	18	
13[b]	$PdCl_2(PPh_3)_2$	*i*PM*t*BA	2.0	8	
14	$PdCl_2(PPh_3)_2$	*i*PM*t*BA	1.5	26	
15	$PdCl_2(PPh_3)_2$	*i*PM*t*BA	1.1	26	59
16	$PdCl_2(PPh_3)_2$	*i*PM*t*BA	1.0	26	
17[c]	$PdCl_2(PPh_3)_2$	*i*PM*t*BA	1.0	24	
18[d]	$PdCl_2(PPh_3)_2$	*i*PM*t*BA	1.1	20	

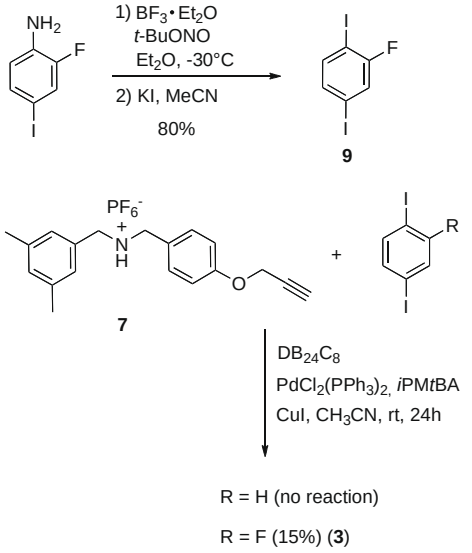
[a] Typical reaction uses CuI (0.04 equiv), Pd (0.02 equiv), DB24C8 (1.20 equiv) and base in acetonitrile (0.2 M) at room temperature.
[b] 2.0 equiv of DB24C8 were added for this entry.
[c] The base was added dropwise to the reaction mixture.
[d] The reaction was started at 0 °C for 1 h.
[e] Me_2NAr = *N*,*N*-dimethylaniline.
[f] *i*PM*t*BA = *N*-isopropyl-*N*-methyl-*tert*-butylamine.
[g] ^1H NMR yields.

the formation of the latter is rather limited by the low efficiency of the pseudorotaxane formation under the various reaction conditions used and not by the efficiency of the Sonogashira coupling itself. It is noteworthy that the yields reported in Table 1 for compound **2** are NMR yields calculated by integrating the methyl group of the blocker on the residual materials obtained after the purification of compound **1**. The purification of compound **2** by column chromatography proved to be unsuccessful because of the great similarity in R_f values for compounds **2** and **7**.

Although the best yield we obtained for the formation of compound **1** is fairly low, we decided to proceed to the synthesis of the [3]rotaxane using the conditions described in the entry 15 of Table 1 (Scheme 2).[15]

First, we have attempted the reaction with 1,4-diiodobenzene as the central rotaxane unit. Unfortunately, this compound is poorly soluble in acetonitrile making the reaction very difficult to proceed. Then, we have decided to use an unsymmetrical diiodophenyl derivative, namely 2-fluoro-1,4-diiodobenzene, in order to increase the solubility. Using the reaction conditions of entry 15, the best yield obtained for the preparation of the [3]rotaxane (compound **3**) is 15%. It is worth mentioning that compound **3** shows very similar R_f on silica TLC plate than that of DB24C8, making the purification rather difficult. Column chromatography followed by preparative size-exclusion chromatography (BioBeads® S-X3) was necessary to obtain compound **3** in good purity. Unfortunately, all attempts to obtain single crystal from compound **3** failed. Counter-anion exchange and acetylation of compound **3** is underway in order to get crystalline derivatives.

In conclusion, we successfully synthesized [2]- and [3]rotaxanes using Sonogashira coupling. Even after optimization of the reaction conditions, the yields are still moderately low. This can be attributed to the steric hindrance provided by the crown ether macrocycle near the reaction site. Fortunately, this reaction was efficient enough to provide our target molecules **1** and **3** in a good purity. The synthesis of new derivatives with longer spacer between the alkyne and the crown ether along with the solid-state NMR studies of compound **3** are underway to test this new molecule as a supramolecular rotor.



Scheme 2. Synthesis of [3]rotaxane-based rotors **1** and **3**.

Acknowledgments

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Supplementary data

Supplementary data (complete synthetic procedures and spectral data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.101.

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15. *Synthetic procedure for compound* **3**. A 10 mL round-bottomed flask under nitrogen atmosphere was charged with a magnetic stir bar, compound **7** (200 mg, 0.47 mmol), dibenzo-24-crown-8-ether (253 mg, 0.56 mmol) and diiodide **9**. Degassed acetonitrile (2.4 mL) was added and the solution was stirred for 15 min prior to the addition of $PdCl_2(PPh_3)_2$ (13 mg, 0.02 mmol) and copper iodide (4 mg, 0,02 mmol). Degassed *N*-isopropyl-*N*-methyl-*tert*-butylamine (67 mg, 0.52 mmol) was then added and the mixture was stirred overnight at room temperature. Dichloromethane (30 mL) was added and the organic layer was washed with water. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel with 5% acetonitrile in dichloromethane as eluent, followed by size exclusion chromatography on Bio-Beads® S-X3 with $CHCl_3$ as eluent to afford 59 mg of [3]rotaxane (**3**) in 15% yield. ^{1}H NMR ($CDCl_3$): 7.47 (br s, 4H), 7.38–7.30 (m, 5H), 7.16 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 9.3 Hz, 2H), 6.88–6.79 (m, 24H), 4.88 (s, 2H), 4.85 (s, 2H), 4.56 (q, J = 6.6 Hz, 4H), 4.41 (t, J = 11.0 Hz, 4H), 4.08 (br s, 16H), 3.74 (m, 16H), 3.44 (m, 16H), 2.12 (br s, 12H); ^{13}C NMR ($CDCl_3$): 162.2 (d, J = 252 Hz, 1C), 158.7 (2×), 147.5 (8×), 138.6 (4×), 133.7, 131.6 (2×), 131.1 (4×), 130.6 (2×), 127.8 (d, J = 3.4 Hz, 1C), 126.6 (4×), 124.7 (2×), 124.7 (2×), 124.5 (d, J = 9.2 Hz, 1C), 121.6 (8×), 118.6 (d, J = 22.8 Hz, 1C), 115.0 (4×), 112.6 (8×), 111.4 (d, J = 15.4 Hz, 1C), 90.8 (d, J = 3.1 Hz, 1C), 86.9, 85.3 (d, J = 3.0 Hz, 1C), 80.2, 70.6 (8×), 70.1 (8×), 68.2 (8×), 56.4 (2×), 52.4, 52.0, 21.2 (4×); ^{19}F NMR ($CDCl_3$): 73.6 (d, $J_{\neq}$ = 714.5 Hz, 12F), 110.3 (dt, J = 7.2 Hz, J = 2.8 Hz, 1F); HRMS m/z 1548.7606 $[M - P_2F_{12}]^+$, (calcd for $C_{92}H_{109}N_2O_{18}$, 1548.7654).