Tetrahedron Letters 59 (2018) 1023–1027

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of star-shaped pyrrole-based C_3-symmetric molecules *via* ring-closing metathesis, Buchwald–Hartwig cross-coupling and Clauson–Kaas pyrrole synthesis as key steps

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ARTICLE INFO

Article history:
Received 26 December 2017
Revised 24 January 2018
Accepted 28 January 2018
Available online 31 January 2018

Keywords:
Trimerization
Ring-closing metathesis
Buchwald–Hartwig cross-coupling reaction
Clauson–Kaas pyrrole synthesis

ABSTRACT

We have demonstrated three contrasting synthetic strategies to assemble pyrrole-based C_3-symmetric molecule. Here, ring-closing metathesis (RCM), Buchwald–Hartwig cross-coupling and Clauson–Kaas pyrrole synthesis have been used as key steps. Interestingly, readily available starting materials such as 4-aminoacetophenone, 4-bromo acetophenone and 4-nitro acetophenone have been used as starting materials. Grubbs' first generation catalyst (G-I) is useful for one-pot RCM and aromatization sequence without the involvement of additional reagents. We also report photophysical properties of these star-shaped molecules.

Introduction

Trimerization of carbonyl compounds is instrumental to assemble C_3-symmetric star-shaped molecules and they are found to be useful core units in conjugated dendrimers[1] and branched oligomers.[1,2] Moreover, conjugated star-shaped molecules have been used in liquid crystals,[3] photovoltaics,[4] organic field-effect transistors (OFETs),[1b,5] organic light-emitting diodes (OLEDs),[1b,6] electroluminescent devices[2a] and organic solar cells.[6a,7] Several C_3-symmetric molecules containing heterocycles (eg: carbazole, and *N*-heterocyclic carbenes) have been synthesized and utilized in electro-optical materials, and separation science.[8] As part of our major program aimed at designing star-shaped C_3-symmetric molecules,[1a,9] here, we conceived new strategies to pyrrole-based C_3-symmetric molecules.

Synthesis of pyrrole derivatives is of great interest due to their applications in material science and pharmaceutical area. In addition, a number of biologically important molecules contain pyrrole as a core unit (Fig. 1).[10] For example, pyrrole moieties have played an important role in haemoglobin function to carry the oxygen in living organisms.[11] Pyrrole derivative, atorvastatin is used for reducing the cholesterol level and ketorolac has been used as non-steroidal anti-inflammatory drug (NSAID).[12]

The metathesis strategy has emerged as one of the most useful tool for the carbon-carbon bond formation in synthetic organic chemistry. Ring-closing metathesis (RCM) is well suited to prepare the cyclic olefins in high yield.[13] With the advent of structurally well-defined ruthenium based metathesis precatalysts (Fig. 2) during the last two decades, assembly of heteroaromatics by intra and intermolecular C—C bond formation has gained momentum.[14]

In view of the importance of pyrroles, we conceived several strategies to C_3-symmetric molecule **4** containing three pyrrole units. To the best of our knowledge there is no report available in the literature to the synthesis of pyrrole-based C_3-symmetric star-shaped molecules. In our approach, pyrrole-based C_3-symmetric star-shaped molecules are assembled by RCM, Buchwald–Hartwig cross-coupling[15] and Clauson–Kaas pyrrole synthesis[16] as key steps. We also studied photophysical properties of these C_3-symmetric molecules.

Strategy

The retrosynthetic strategy to pyrrole-based star-shaped compound **4** is shown in Fig. 3. C_3-Symmetric star-shaped compound **4** could be assembled from hexa-allyl derivative **3** via RCM followed by aromatization. The hexa-allyl derivative **3** could be assembled from di-allyl ketone **2** by trimerization sequence which can be derived from readily available 4-amino acetophenone (**1**) (path A). Alternatively, C_3-symmetric product **4** could be assembled

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https://doi.org/10.1016/j.tetlet.2018.01.084
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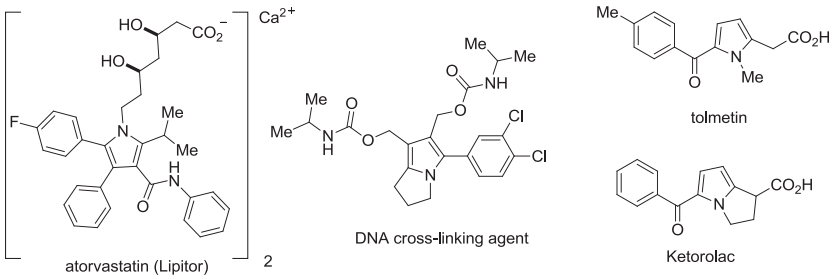

Fig. 1. Bio-active molecules containing pyrrole moieties.

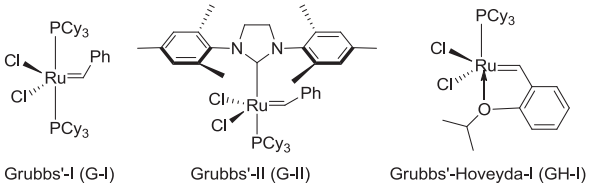

Fig. 2. Selected list of ruthenium-based metathesis catalysts.

from C_3-symmetric tri-bromide **5** (Fig. 3) via Buchwald–Hartwig cross-coupling reaction. However, the tri-bromo derivative **5** can be derived from a readily available 4-bromo acetophenone (**6**) by trimerization sequence. These three distinctly different approaches provide several opportunities to expand the chemical space of C_3-symmetric pyrrole derivatives. Finally, application of three fold Clauson–Kaas pyrrole synthesis starting with **5** can generate the target compound **4**.

Results and discussion

To realize the strategy shown in Fig. 3 (Path A), commercially available 4-amino acetophenone (**1**) was treated with allyl bromide in the presence of sodium hydride (NaH) in dimethylformamide (DMF) at room temperature for 1 h which delivered the *N*,*N*'-diallyl product **2** (68%). Then, the di-allyl compound **2** was subjected to trimerization sequence with thionylchloride ($SOCl_2$) in EtOH under reflux condition to generate the trimerized product **3** in 42% yield. To improve the yield of the compound **3,** we choose another route. In this regard, we prepared tri-amine derivative **9** by using literature procedure.[17] Star-shaped tri-amine derivative **9** was subjected to *N*-allylation by using allyl bromide in the presence of NaH in DMF at room temperature for 2 h to give the hexa-allyl product **3** in 72% yield. Later, it was treated with Grubbs first generation catalyst (G-I) in CH_2Cl_2 at room temperature for 2 h to obtain the ring-closing metathesis (RCM) product **4** (84%) which underwent aromatization. The major driving force for facile dehydrogenation sequence under the reaction conditions is the gain in aromatization energy (Scheme 1). Such type of non-metathetic behaviour of Grubbs catalyst is known in the literature.[18] Notably, earlier approach to pyrroles[19] involving RCM require separate step for aromatization. Interestingly, our approach involving G-I catalyst does not require aromatization step which is better sustainable sequence.

Later, alternate routes were developed to this star-shaped pyrrole containing compound **4**. In this regard, compound **9** was reacted with 1,4-dimethoxy tetrahydrofuran (**10**) in acetic acid under reflux condition for 6 h to deliver the pyrrole-based C_3-symmetric compound **4** in 63% yield (Scheme 2).

In another route, we prepared the tri-bromo derivative **5** by using the literature procedure from commercially available 4-bromo acetophenone (**6**).[20] Subsequently, the tri-bromo compound **5** was subjected to Buchwald–Hartwig cross-coupling reaction with pyrrole (**11**) in the presence of potassium carbonate (K_2CO_3) and, copper powder in dimethyl sulfoxide (DMSO) at 130 °C under inert atmosphere to obtain the star-shaped molecule **4** in 68% yield (Scheme 3). The approaches demonstrated here start with simple

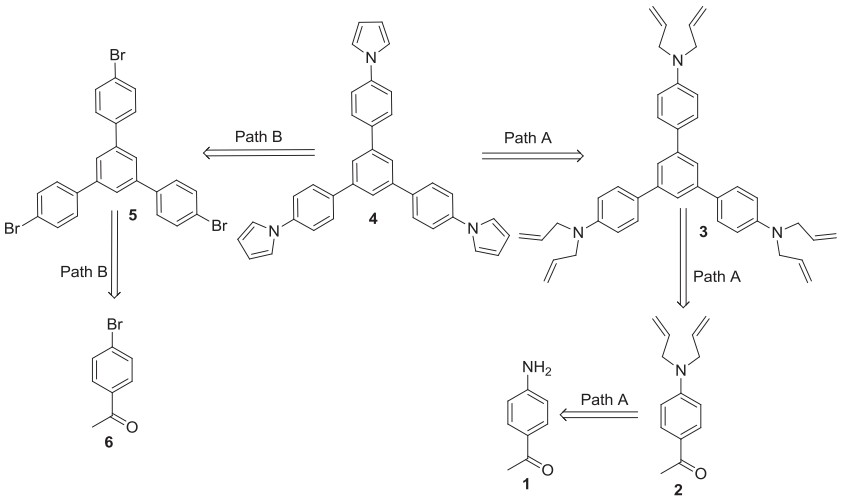

Fig. 3. Retrosynthetic routes to pyrrole-based C_3-symmetric star-shaped molecule **4**.