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STEP-BY-STEP SYNTHESIS OF UNSYMMETRICALLY SUBSTITUTED PYRANOISOCOUMARINS FROM TEREPHTHALIC ACID

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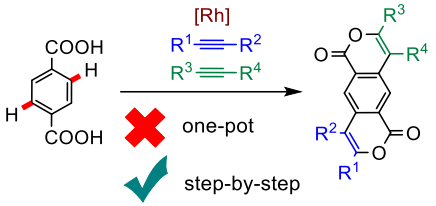
Abstract

An efficient multi-step protocol for the selective synthesis of unsymmetrically substituted pyranoisocoumarins (pyrano[3,4-*g*]isochromene-1,6-diones) has been developed. The procedure includes the two-fold step-by-step C–H annulation of terephthalic acid with two different alkynes. The photophysical properties of pyranoisocoumarins were predicted by DFT calculations.



Key words: C–H activation, isocoumarin, pyranoisocoumarin, homogeneous catalysis, rhodium.

Introduction

Isocoumarins are a widespread class of heterocyclic organic compounds, many of which occur in nature [1–4]. Meanwhile, various substituted and π-extended isocoumarins may exhibit good bipolar-transporting and luminescence properties that allow them to be used as light-emitting materials or dopants in OLED devices [5–7]. At the same time, C–H activation/annulation of readily available aromatic compounds (such as benzoic acids) with alkynes, catalyzed by rhodium(III) complexes, turned out to be the most step- and atom-economic method for the synthesis of heterocyclic compounds [8, 9]. In particular, this method was used for the synthesis of the first example of symmetrically substituted pyranoisocoumarins from terephthalic acid and 4-octyne in one step (Fig. 1a) [10].

Earlier we have shown that the synthesis of pyranoisocoumarins from terephthalic acid is often complicated by the side formation of π-extended isocoumarins as a result of decarboxylation of one carboxylic group (Fig. 1b) [11]. Moreover, it should be noted that in the case of diphenylacetylene, the formation of the π-expanded isocoumarin becomes the preferred reaction pathway. Another disadvantage of this approach is the inability to selectively introduce two different alkynes. Herein, we report the synthetic protocol for unsymmetrically tetra-substituted pyranoisocoumarins *via* Rh(III)-catalyzed two-fold step-by-step C–H annulation of terephthalic acid with two different alkynes (Fig. 1c).

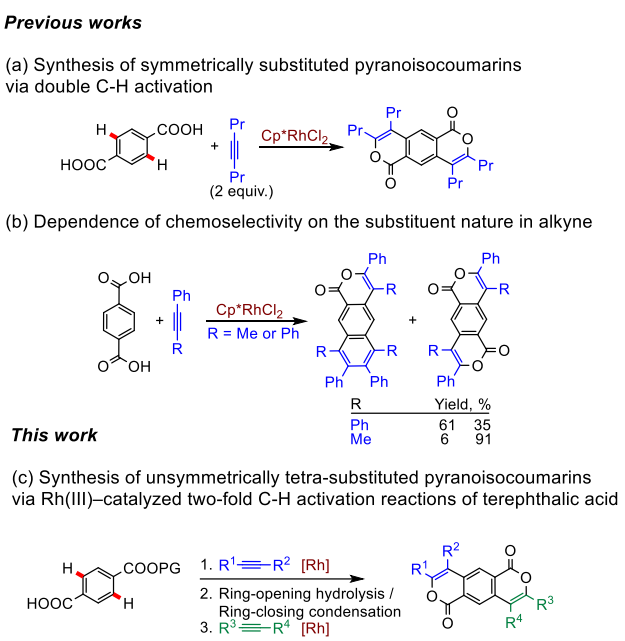
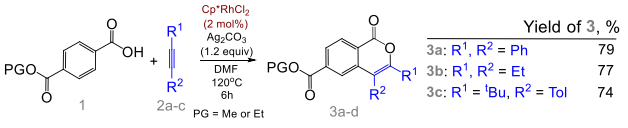


Figure 1. Synthetic strategies towards diisocoumarins.

Results and discussion

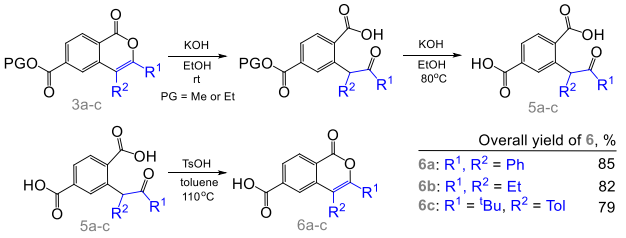
First of all, to protect one of the carboxyl groups, we prepared monoalkyl ester **1** by the exhaustive esterification of terephthalic acid followed by the selective hydrolysis of diethyl terephthalate obtained [12]. Subsequent Rh(III)-catalyzed C–H activation/annulation of **1** with the first alkyne coupling partner **2a**–**c** afforded 3,4-substituted isocoumarins **3a**–**c** with an ester group at the sixth position (Scheme 1). Reactions were carried out under previously described conditions using Ag_2CO_3 as an oxidant [11] and proceeded with high yields and selectivity. The selectivity of *ortho*-CH activation is provided by the coordination of rhodium to the carboxyl group, which acts as a directing group. In the reaction with tolane **2a**, only a small admixture of naphthalene derivative **4a** was formed (see the Electronic supplementary information (ESI)). The annulations



Scheme 1. Rh-catalyzed C–H activation/annulation of **1** with the first alkyne coupling partner.

with alkynes containing alkyl groups, such as diethylacetylene and 1-(3,3-dimethylbut-1-yn-1-yl)-4-methylbenzene, resulted in the formation of only isocoumarin products.

In order to remove the protecting ester group, we tried to hydrolyze isocoumarins **3a**–**c**. However, it was found that the hydrolysis is also accompanied by the cleavage of the lactone ring, giving *ortho*-substituted terephthalic acids **5a**–**c**. The latter can be cyclized back in the presence of *p*-TsOH with the formation of target 6-carboxy-substituted isocoumarins **6a**–**c** (Scheme 2).

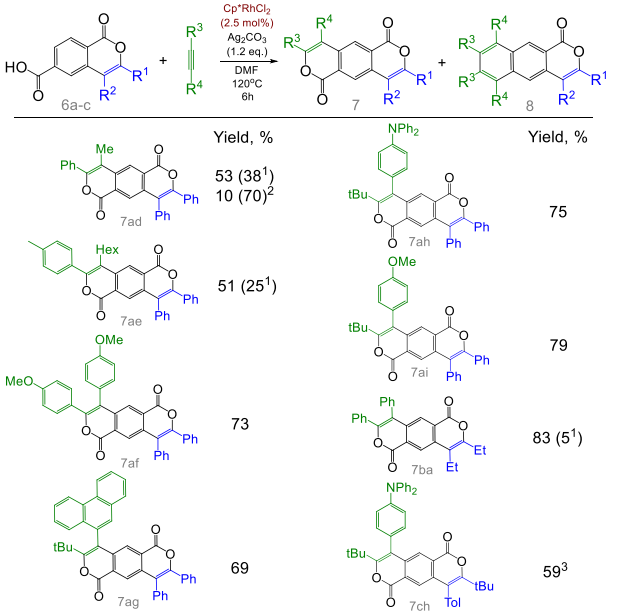


Scheme 2. Synthesis of isocoumarins **6a–c** *via* ring-opening hydrolysis/ring-closing condensation of **3a–c**.

Finally, rhodium(III)-catalyzed C–H activation/annulation of **6a**–**c** with the second alkyne coupling partner resulted in desired unsymmetrically substituted pyranoisocoumarins **7** in good to high yields (Scheme 3). The regioselectivity of alkyne insertion is provided by competing electronic (preferred orientation of the aryl substituent to the third position of an isocoumarin) and steric factors (preferred orientation of the bulky ^{t}Bu group to the third position).

Interestingly, in the case of coupling of **6a** with 1-phenyl-1-propyne **2d**, we observed the side formation of π-extended isocoumarin **8ad** in 38% yield as a result of the decarboxylation. Moreover, in the case of $[CpRhI_2]_n$ used as a catalyst, which usually promotes the decarboxylation process [5, 11, 13], π-extended isocoumarin **8ad** becomes the major product. 1-Methyl-4-(oct-1-yn-1-yl)benzene **2e** reacts in a similar manner, giving a 2 to 1 mixture of **7ae** and **8ae**. In contrast, alkynes **2g**–**2i**, containing bulky ^{t}Bu group, lead to the selective formation of pyranoisocoumarins **7ag**–**7ai** and **7ch** since the decarboxylation and insertion of a second alkyne molecule is unfavorable in this case due to high steric hindrance.

We have previously demonstrated that isocoumarins do not have pronounced donor-acceptor properties and can therefore act as both a donor and an acceptor unit in D–A (donor-acceptor) type molecules [14–16]. Accordingly, in the presence of such classical donors as the *p*-(diphenylamino)phenyl substituent [17, 18], an isocoumarin moiety should exhibit acceptor properties. Indeed, our DFT and TD-DFT calculation data at the B3LYP/6-31G(d) level showed that the first singlet excited state (S_1) in **7ah** and **7ch** has the charge-transfer nature, where the HOMO orbital is located on the triphenylamine moiety, while the LUMO orbital is on the isocoumarin moiety. Moreover, it is important to note that bulky ^{t}Bu groups in these compounds can prevent intramolecular rotation to maintain the orthogonal structure, which is necessary to decrease the energy gap between the first triplet and singlet excited states. The latter is one of the requirements for materials for the construction of OLED devices with the TADF effect [19–21].



Scheme 3. Rh-catalyzed C–H activation/annulation of **6a–c** with the second alkyne coupling partner. [1] Yields of **8**. [2] $[CpRhI_2]_n$ as a catalyst. [3] ^{t}AmOH as a solvent.

Conclusions

In summary, we developed the multi-step synthetic approach to unsymmetrically substituted pyranoisocoumarins starting from readily available terephthalic acid and alkynes. Although the key steps of the rhodium-catalyzed C–H activation tolerate various functional groups, the selective insertion of two different alkynes requires the protection of one carboxylic group in terephthalic acid. Utilizing the coupling alkynes bearing strong donor substituents, the method allows for obtaining the D–A luminophores with charge transfer character of the excited state S_1, in which the pyranoisocoumarin moiety acts as an acceptor unit.

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Electronic supplementary information

Electronic supplementary information (ESI) available online: the details of synthetic procedures and DFT calculations, NMR spectra for the compounds obtained and atomic coordinates for the optimized geometries. For ESI, see DOI: 10.32931/io2516a.

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