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Co(I) catalyzed yne-ene-yne [2+2+2] cycloaddition: synthesis of highly strained pentacyclic bis-lactones. A new access to tetraaryl *N*-hydroxyphthalimides



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ABSTRACT

Highly strained pentacyclic bis-lactones can be obtained by an unusual Co(I) catalyzed [2+2+2] cycloaddition of an yne–ene–yne diester substrate. These bis-lactones can be further transformed into tetraaryl *N*-hydroxyphthalimides which are potential aerobic oxidation organocatalysts. © 2014 Elsevier Ltd. All rights reserved.

N-Hydroxyphthalimide (NHPI, Fig. 1) has been recognized as a valuable organocatalyst for the aerobic oxidation of various organic compounds under mild conditions.¹ However, the major drawback of this system is the rather low turnover number of NHPI, requiring typically 10 mol % of catalyst to obtain good conversions (thus limiting its use on a large scale). Our group, among others, has been engaged in the synthesis of NHPI analogs having improved or new catalytic properties.² The best catalyst we have obtained so far is the simple tetraphenyl analog (NHTPPI, Fig. 1) with which a 10-fold decrease in catalyst loading (i.e., 1 mol %) can be achieved.^{2a} Consequently, we have further developed methods giving access to other polyarylated phthalimides,³ and we wish to report in this Letter a new route to such compounds via the [2+2+2] cycloaddition of yne–ene–yne linear substrates.

The [2+2+2] cycloaddition of three alkynes is a very powerful and elegant method for the formation of highly substituted benzene rings⁴ and among the many transition metal catalysts used, cobalt occupies a prominent place.⁵ This led us to devise a route to substituted analogs of NHTTPI, based on the cobalt catalyzed intramolecular cycloaddition of a triyne (Scheme 1).

The obvious substrate for the planned cycloaddition is triyne ester **1** (Fig. 2). However, although simple acetylene dicarboxylic esters like methyl, ethyl, or butyl are commercially available, esterification of acetylene dicarboxylic acid (ADA) is noteworthily



Figure 1. Structure of NHPI and NHTPPI.



Scheme 1. Retrosynthetic analysis of tetraaryl N-hydroxyphthalimides.



Figure 2. Structure of triyne ester 1.



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difficult as the triple bond is very electrophilic, thus leading to conjugate addition products rather than the expected esters.⁶ Indeed, all our attempts to synthesize ADA esters of suitably functionalized phenols failed.

We then imagined installing the carboxyl functions after the cycloaddition. We thus readily prepared triyne ether **2** by condensation of *ortho*-ethynylphenol⁷ with 1,4-dichlorobutyne and submitted it to the cobalt catalyzed cycloaddition under classical reaction conditions⁵ (light irradiation in refluxing toluene) to access the expected pentacyclic bis-benzochromene **3** in 62% yield (Scheme 2). This first result was very interesting as it gave an easy access to the highly substituted aromatic nucleus needed. Unfortunately, all our attempts to fully oxidize **3** to the bis-chromene-6-one **5** failed. In the best case, using conditions reported for the oxidation of parent mono-benzochromene⁸ only traces of bis-lactone **5** were obtained, in 36% yield of the mono-oxidized product **4**.

As our first two strategies failed, we envisaged to prepare fumaroyl esters of type **6** and engage them in the [2+2+2] cycloaddition (Scheme 3). But although the total intramolecular cycloaddition of acyclic triynes⁹ and ene–diynes¹⁰ is rather well known, the use of the linear yne–ene–yne sequence is much less common.¹¹

We have thus prepared yne-ene-yne **6a** by condensation of ortho-ethynylphenol with fumaroyl chloride (Scheme 3). This linear substrate was then subjected to the classical Co(I) cycloaddition in refluxing toluene, under visible light irradiation.¹² In this case, a stoichiometric amount of cobalt catalyst is necessary, as the intermediate cyclohexadiene is a very good ligand of Co(I). After the oxidative decomplexation/aromatization of the cyclohexadienyl-cobalt(I) intermediate, we were pleased to obtain bis-lactone 5a in an encouraging 25% yield for two steps and the formation of three C–C bonds. After many attempts, a maximum of 30% yield could be obtained.¹³ This yield can seem low but it appears that bis-lactone **5a** is rather unstable during chromatographic purification and thus, part of the product is lost during purification.¹⁴ The X-ray diagram of **5a**¹⁵ shows a very strained structure: as the two lactone carbonyl groups are pointing toward each other, steric and electronic repulsion implies an out of plane deformation of the central aromatic nucleus. The dihedral angle of the planes containing the two C=O is 40° and their O-O



Scheme 2. Synthesis and [2+2+2] cycloaddition of triyne ether 2.



Scheme 3. Synthesis and [2+2+2] cycloaddition of yne-ene-yne 6a.

distance is 2.78 Å, indicating a *trans* conformation of the two lactones as expected.

After this first successful reaction, we wanted to explore the scope of this new methodology, and started with variation of the R substitution at the alkynes (Table 1). Replacement of the phenyl terminal group by a TMS or iodine (entry 2 and 3) does not lead to any cyclized product but to extensive decomposition. A first possible explanation based on the steric hindrance was ruled out by the fact that the terminal alkyne (R = H) does not give any cyclized product either (entry 4), whereas a butyl chain led to 5% of the corresponding dilactone **5e**.

These first results indicating the need for a terminal aromatic group, we then prepared enediynes **6f** and **6g**, whose terminal aromatic is substituted respectively by a *para*-methoxy and a *para*-trifluoromethyl group. In the case of the electronically enriched **6f**, the cylotrimerization proceeds in a better 40% yield (entry 6) compared to the nonsubstituted case, and in only 5% yield for electron poor **6g** (entry 7).

Our next questioning was whether the geometry of the central double bond plays an important role in the outcome of the



Entry	R	Isolated yield
1	6a , Ph	5a , 30%
2	6b , TMS	_
3	6c , I	_
4	6d , H	_
5	6e , Bu	5e , 5%
6	6f , <i>p</i> -MeOPh	5f , 40%
7	6g , <i>p</i> -CF ₃ Ph	5g , 5%

reaction. Indeed, when enediyne **6a** is reacted with cobalt(I), either metalacyclopentene **A** or metalacyclopentadiene **B** can be formed but both pathways lead to the same *trans* configuration of the cyclohexadienyl cobalt complex **C** (Scheme 4).¹⁶ In the first case the *trans* configuration is set during the alkyne–alkene oxidative coupling, whereas in the second case it comes from the insertion of the *E* double bond in the metalacyclopentadiene formed by al-kyne–alkyne oxidative coupling.

If the same reasoning is applied to the Z analog of **6a**, then a very crowded *cis*-cyclohexadienyl cobalt complex **D** would be formed, in which the two carbonyl groups would be facing each other on the same side of the cycle. Although aromatization of **D** will lead to the same lactone **5a**, going through this intermediate would be a highly energetic, hence unfavorable pathway. Indeed, when **7** is reacted with Co(I), the *trans* bis-lactone **5a** is obtained in a very low 4% yield (Scheme 5). The hypothesis of an *E* to *Z* isomerization of the central double bond by light irradiation can be ruled out as, after refluxing yne–ene–yne **7** alone in toluene under light irradiation, the product is recovered unchanged.



Scheme 4. Possible [2+2+2] cycloaddition routes of yne-ene-yne 6a.



Scheme 5. [2+2+2] Cycloaddition of yne-ene-yne 7.



Scheme 6. Synthesis of N-hydroxyimide 8.



Scheme 7. Catalytic evaluation of N-hydroxyimide 8.

Finally, lactone **5a** was converted to hydroxyimide by reaction with hydroxylamine, affording the first substituted NHTPPI **8** in 40% yield (Scheme 6). Unfortunately, the first oxidation tests performed with this compound have shown a very low catalytic activity (Scheme 7), probably due to the presence of the free phenols which can inhibit the radical mechanism associated with NHPI^{1a} through the formation of phenoxyl radicals.¹⁷

In conclusion, we have explored the synthesis of highly strained pentacyclic bis-lactones by an unusual cobalt(I) catalyzed [2+2+2] cyclization of an yne–ene–yne linear fragment. Although the scope of the reaction is rather narrow, we have been able to prepare **8**, the first substituted analog of NHTPPI. The presence of two *ortho*-OH substituents on the apical phenyl rings also induces the presence of two chirality axes and thus allows a new access to chiral NHPI analogs.^{2b} Further derivatization of these phenol functionalities is under way in our laboratory for the study of the catalytic properties of these derivatives.

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Supplementary data

Supplementary data (experimental procedure as well as characterization of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/ j.tetlet.2014.03.081.

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- 12. Typical [2+2+2] cyloaddition procedure: To a degassed solution of enediyne (1 mmol) in distilled toluene (10 mL) was added CpCo(CO)₂ (133 µL, 1 mmol) at room temperature under argon. The mixture was then refluxed under argon and irradiated using a 500 W halogen lamp, until completion of the reaction (monitored by TLC, typically 4–7 h). After cooling to room temperature, a solution of FeCl₃-6H₂O (1.5 g, 5 mmol) in acetonitrile (5 mL) was added. After 10 min of stirring at room temperature, TLC shows the disappearance of the cobalt–cyclohexadiene complex red spot and appearance of a slightly more polar spot, greenish under narrow UV (365 nm) irradiation, corresponding to the aromatized product. After evaporation of the solvents, purification of the crude by flash chromatography using a cyclohexane/ethyl acetate gradient (1:0–6:4) provided the product as a yellow solid.
- Cobalt is the metal of choice for such intramolecular cyclization. We also tried Wilkinson catalyst, [RhCl(cod)]₂/DPPE, [IrCl(cod)]₂/DPPE, but no trace of cycloaddition product could be observed in these cases.
- 14. The NMR spectrum of the crude reaction mixture shows a complete conversion. However, the 2D TLC of bis-lactone **5a** shows that this compound decomposes on chromatographic media.
- 15. The ORTEP drawing can be found in the Supplementary material. Crystallographic data (CIF) for 13,14-diphenylbenzo[1,2-c/6,5-c']dichromene-6,7-dione 5a has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 933767. This material is available free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.
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