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Application of the Nicholas reaction to the synthesis of dicobalt hexacarbonyl complexed diyne ethers

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ABSTRACT

Addition of propargylic or homopropargylic ynols to dicobalt hexacarbonyl propargylium cations gave the expected ether products of the Nicholas reaction, with the exception of 4-phenyl-3-butyn-1-ol which gave a dihydrofuran due to propargylium cation promoted 5-endo ring-closure. Use of chiral dicobalt hexacarbonyl complexed propargylic ynols as both propargylium cation precursor and nucleophile gave racemic doubly complexed disymmetric diyne ethers, each as a single diastereoisomer. Addition of dicobalt hexacarbonyl complexed 1-phenyl-1-butyne-3-ene to the propargylium cation derived from dicobalt hexacarbonyl complexed 1-phenyl-1-butyn-3-ol, followed by the addition of a nucleophile (NuH), gave double complexed 1,7-diphenyl-3-Nu-5-methylhepta-1,6-diynes (*d.r.* > 10:1).

Introduction

Transition metal catalysed [2 + 2 + 2] cyclotrimerisation is a valuable procedure for the synthesis of arenes [1], including bicyclic compounds generated from linked diyne precursors (Scheme 1 – [a]) [2]. In a related process, that also proceeds *via* an intermediate metallocyclopentadiene [3], we have reacted ether and ester linked chiral diynes with (η^5-cyclopentadienyl)cobaltdicarbonyl to give planar chiral cyclopentadienone metallocenes with moderate diastereoselectivity (Scheme 1 – [b]) [4]. In an extension of this chemistry we chose to explore the possibility of employing cobalt for the synthesis of ether linked diynes by utilisation of the Nicholas reaction starting from a dicobalt hexacarbonyl complexed propargylic alcohol (Scheme 1 – [c]) [5]. Subsequent generation of an intermediate metal-stabilised propargylium cation followed by addition of a nucleophile has been demonstrated repeatedly [6], but the use of ynols in this reaction is limited [7]. In this paper we describe our studies in this area, including the use of dicobalt hexacarbonyl complexed propargylic alcohols as nucleophilic components in a highly diastereoselective synthesis of C_2-symmetric doubly-complexed diyne ethers.

A series of propargylic alcohols **1a–d** were complexed by stirring with dicobalt octacarbonyl in dichloromethane at room temperature to give **2a–d** in high yield (Scheme 2). Treatment of **2a** with boron trifluoride etherate in dichloromethane at 0 °C gave the corresponding propargylium cation *in situ*. Addition of 2-propyn-1-ol or 3-phenyl-2-propyn-1-ol followed by aqueous sodium hydrogencarbonate work-up and chromatography resulted in the isolation of mono-complexed diyne ethers **3** and **4** respectively (Scheme 3).

Further application of this procedure, with the objective of generating the homologue of **4**, had a different outcome (Scheme 4). Addition of 4-phenyl-3-butyn-1-ol to the *in-situ* generated propargylium cation from **2a** resulted in dihydrofuran **5** as the sole isolable product identified, in-part, by the absence of signals for uncomplexed alkyne carbons in the ^{13}C NMR spectrum. Instead signals at 112.7 and 127.6 ppm were assigned to the alkene functionality resulting from electrophile promoted nucleophilic closure *via* **6** to give the 5-endo cyclisation product [8]. In the absence of the 4-phenyl substituent on the alkyne, the expected Nicholas-type reaction proceeded as expected with 3-butyn-1-ol giving adducts **7** and **8** from complexes **2a** and **2b** respectively (Scheme 5). Subsequent Sonogashira cross-coupling with iodobenzene introduced the 4-phenyl substituent and enabled the isolation of **9**, the target of the reaction that resulted in dihydrofuran **5**. The same sequence of reactions starting with **2b** resulted in the isolation of complex **10**.

In addition to using the dicobalt hexacarbonyl–alkyne complexes as precursors to intermediate propargylium cations, we also wished to explore the use of these as nucleophilic components in these ether formation reactions. Although the reaction of a propargylic alcohol with the cation generated from it to give a

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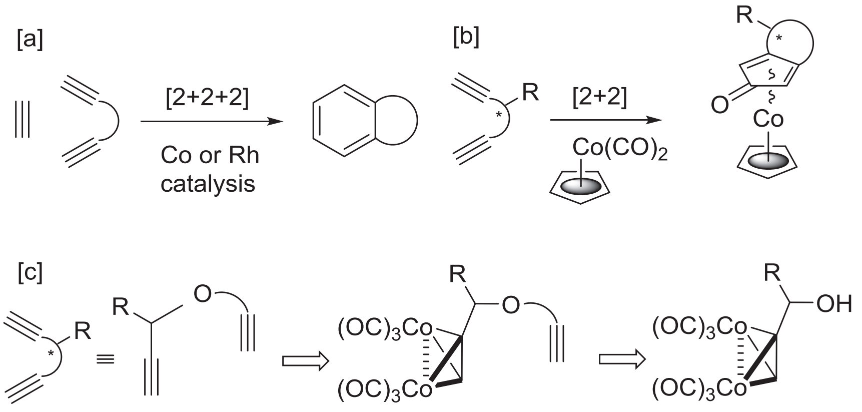
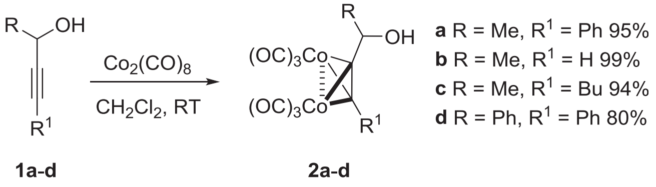


Scheme 1. Linked Diynes. Uses [a,b] and proposed method of synthesis [c].

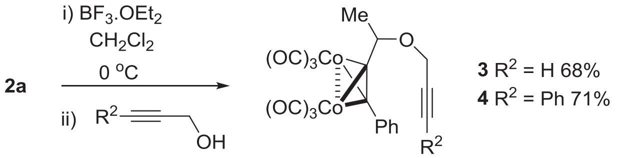
symmetrical ether has been observed [7], the stereochemistry of this reaction does not appear to have been reported. To this end, and to ensure compete conversion to the intermediate carbocation, fluoroboric acid was added to complex **2a** in ether at −35 °C. After isolation of the resulting propargylium salt by filtration, dissolution in dichloromethane followed by the addition of a further equivalent of **2a** gave the doubly-complexed diyne ether adduct **11** in good yield, and as a single isomer as determined by ^{1}H NMR spectroscopy (Scheme 6). An X-ray crystal structure analysis revealed the relative configuration as R^*, R^* (Fig. 1). The formation of a single isomer from racemic starting materials is a consequence of the stereochemical lability of the intermediate dicobalt hexacarbonyl propargylium cation due to the antarafacial migration of an alkylidene moiety from one cobalt tricarbonyl unit to the other [9]. Rapid racemisation and minimisation of steric interaction as represented in Scheme 7 explains the observed selectivity for the C_2-isomer.

When this protocol was repeated with **2b**, the doubly complexed diyne ether **12** was also obtained as a single isomer, and the same relative stereochemistry confirmed by X-ray crystallography (Fig. 2, *S**, *S**-isomer shown). Boron trifluoride etherate may also be used to generate the intermediate propargylium cation, as demonstrated with the butyl-substituted starting material **2c** which gave only doubly complexed diyne ether **13**, with the stereochemistry assigned by analogy to **11** and **12** (Scheme 8).

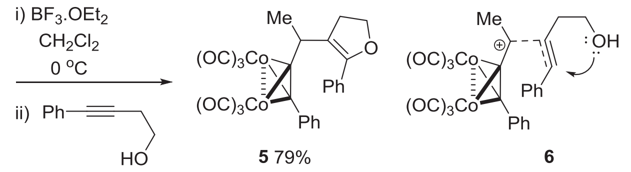
In contrast, a quite different outcome was observed with diphenyl congener **2d** where THF was employed as the solvent to aid solubility in the propargylium cation generation step with fluoroboric acid. Following the addition of a further equivalent of **2d**, an adduct was generated containing a new carbon–carbon bond in a diastereomeric ratio of 12:1 (Scheme 9). Following recrystallisation, the relative stereochemistry of the major isomer was revealed as R^*, R^* by X-ray crystallography (Fig. 3). Related coupling reactions of radicals generated *in situ* in THF from dicobalt hexacarbonyl propargylium cations containing an α-aryl substituent have been reported previously [10,11], the reactions proceeding with high diastereoselectivity to give predominantly racemic C_2-symmetric dimers, as observed in this example [12].



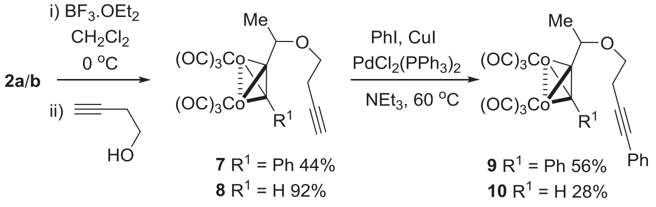
Scheme 2. Synthesis of dicobalt hexacarbonyl complexes **2a**–**d**.



Scheme 3. Synthesis of mono-complexed diyne ethers **3** and **4**.

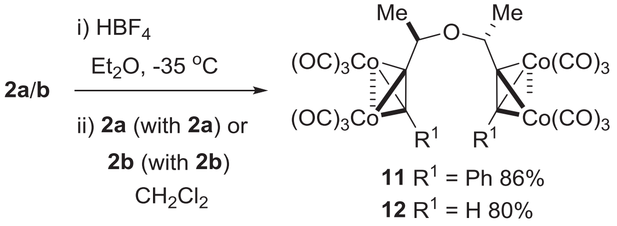


Scheme 4. Generation of dihydrofuran **5**.



Scheme 5. Mono-complexed diyne ether synthesis and subsequent Sonogashira coupling.

During the course of the synthesis of mono-complexed diyne ether **3**, a further complex was isolated in 15% yield identified as doubly-complexed triyne **15** (Fig. 4), apparently as essentially a single diastereoisomer as determined by NMR spectroscopy. A



Scheme 6. Diastereoselective synthesis of doubly-complexed C_2-symmetric diyne ethers **11** and **12**.