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Synthesis of C-Aryldeoxyribosides by [2 + 2 + 2]-Cyclotrimerization Catalyzed by Rh, Ni, Co, and Ru Complexes

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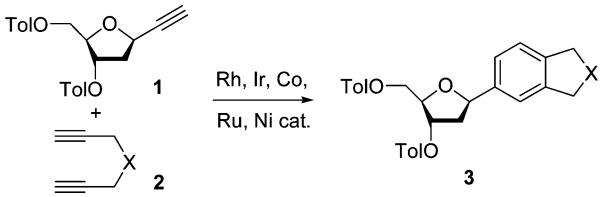
ABSTRACT



A novel approach to the synthesis of functionalized C-nucleosides was developed. Cyclotrimerization of C-alkynyldeoxyriboside with a variety of substituted 1,6-heptadiynes to the corresponding C-aryldeoxyribosides was catalyzed by various transition metal complexes (Rh, Ir, Co, Ru, and Ni). The most general catalyst proved to be $RhCl(PPh_3)_3$, which could catalyze most of the cyclotrimerizations in high yields (52–95%).

C-Nucleosides are an important class of compounds characterized by replacement of a labile nucleosidic C−N bond by a stable C−C bond. Many of them possess antiviral or antineoplastic activities.[1] Quite recently, C-nucleosides bearing hydrophobic aryl groups as nucleobase surrogates attracted great attention due to their use in the extension of the genetic alphabet.[2] Duplexes containing self-pairs of hydrophobic nucleobases are stable due to increased stacking and favorable desolvation energy as compared to canonical nucleobases.[3] Triphosphates of some of the C-nucleosides are efficiently incorporated to DNA by DNA polymerase.[4] There are a number of synthetic approaches to C-nucleosides.[5] The most general methods are (i) additions of organometallics to ribono- or 2-deoxyribonolactones,[4,6] (ii)

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coupling of a halogenose with organometallics,[7] or (iii) electrophilic substitutions of electron-rich aromatics with sugars under Lewis acid catalysis.[8] All these approaches suffer from insufficient anomeric selectivity and the necessity to optimize reaction and separation conditions for each particular C-nucleoside. Very recently, we have developed[9] a modular approach consisting of the preparation of bromophenyl C-nucleosides as versatile intermediates suitable for further derivatization, giving rise to a series of diverse target C-nucleosides. Here we report on another modular approach consisting of construction of an aromatic ring on deoxyribose by cyclotrimerization of 1-ethynyl-2-deoxyribose with α,ω-diynes.

Catalytic cyclotrimerization of alkynes to benzene derivatives is a nice example of an efficient and clean reaction during which three new C−C bonds are formed in one step. As such, it fulfills all standards to define it as an atom economical procedure.[10] Therefore, it is not surprising that it has been used as a key step for the synthesis of a plethora of natural and biologically active compounds and their derivatives.[11] Out of many possible synthetic approaches to C-arylglycosides, the one based on a catalytic [2 + 2 + 2]-cyclotrimerization of α,ω-diynes with C-alkynylglycosides is promising because it can furnish the desired compounds under mild reaction conditions. Moreover, the reaction of pure α- and β-alkynylsaccharides should furnish the corresponding anomers, thus overcoming stereochemistry problems. As far as the application of cyclotrimerization methods in the synthesis of C-arylglycosides is concerned, it has been carried out with various alkynylpyranoses,[12−14] whereas its application for the synthesis of deoxyribose or ribose derivatives has been rather neglected. Our goal was to fill this gap and to test the cyclotrimerization strategy for the preparation of a series of variously substituted C-aryldeoxyribosides, as well as to assess the suitability of various commonly used transition metal catalysts for this reaction. Our initial goal was to prepare pure 1β-ethynyl-1,2-dideoxy-3,5-di-*O*-(4-toluoyl)-D-ribofuranose **1β** according to the reported procedure.[15] Although we followed the protocol precisely, only a 2:1 anomeric mixture of 1α- and 1β-ethynyl-1,2-dideoxy-3,5-di-*O*-(4-toluoyl)-D-ribofuranose, **1α** and **1β**, was obtained each time.

Since the separation of anomeric mixtures required the use of HPLC, we decided to check the catalytic activity of various transition metals complexes for [2 + 2 + 2]-cyclotrimerization with the anomeric mixture **1**. As the second reaction partner, dipropargylmalonate **2a** was chosen. To keep the experimental conditions as simple as possible, all

Scheme 1. Catalytic Cyclotrimerization of **1** with **2a**

1, anomeric mixture;**1α**, α-anomer; **1β**, β-anomer
In compounds **2**, **3**, and **3β**: **a**, X = $C(COOEt)_2$; **b**, X = $C(COMe)_2$; **c**, X = C(COOEt)COMe; **d**, X = C(COOEt)CN; **e**, X = NTs; **f**, X = O

the reactants were stirred in a 3 mL glass vial under protective atmosphere of argon for an appropriate amount of time. The obtained results are presented in Table 1. At

Table 1. Catalytic Cyclotrimerization of an Anomeric Mixture **1** with Diynes **2**[a]

entry	diyne **2**	catalyst	product **3**	yield (%)[b]
1	**2a**	$Rh(PPh_3)_3Cl$	**3a**	86
		$[Ir(COD)Cl]_2$/dppe[c]		42
		$NiBr_2$(dppe)/Zn[c]		44
2	**2b**	$Rh(PPh_3)_3Cl$	**3b**	57
3	**2c**	$Rh(PPh_3)_3Cl$	**3c**	57
4	**2d**	$Rh(PPh_3)_3Cl$	**3d**	52
5	**2e**	$Rh(PPh_3)_3Cl$	**3e**	17
6	**2f**	$Rh(PPh_3)_3Cl$	**3f**	52

[a] The reaction was carried out at 20 °C. [b] Isolated yields. [c] The reaction was carried out at 80 °C.

the ambient temperature (20 °C), only $Rh(PPh_3)_3Cl$ was catalytically active.[16] The use of $[Ir(COD)Cl]_2$/dppe[17] and $NiBr_2$(dppe)/Zn[18,19] required the use of a temperature of 80 °C to promote the reaction (entry 1). The isolated yields of the C-aryldeoxyriboside **3a** were 86, 42, and 44%, respec-

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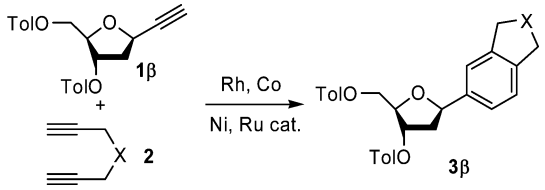
tively. Since the best result was obtained with Wilkinson's catalyst, next we examined the generality of the cyclotrimerization of **1** with differently substituted α,ω-diynes (Table 1, entries 2−6). The reactions with heptadiynes **2b**−**2d** afforded the corresponding C-aryldeoxyribosides **3b**−**3d** in good isolated yields (52−57%). Surprisingly, introduction of nitrogen into the linker connecting the triple bonds, the reaction with dipropargyltosylamide **2e**, yielded the target glycoside **3e** only in low yield of 17%. On the other hand, the reaction with dipropargyl ether **2f** resulted in the formation of **3f** in reasonable yield (52%) (entry 6). In contrast to the above-mentioned results, the cyclotrimerization with 1,7-octadiyne gave only a complex reaction mixture. This observation is not surprising since a similar result has been observed before.[16b]

After the method was optimized with the anomeric mixture **1**, we applied it to pure β-anomer **1*β***. The cyclotrimerizations were carried out with various Ru, Rh, Co, and Ni complexes as representatives of the most widely utilized catalysts to assess their catalytic activity and selectivity (Table 2). Out of them, as expected, $Rh(PPh_3)_3Cl$ (Wilkinson's catalyst) emerged as the most active and general one. The corresponding C-aryldeoxyribosides were obtained from reasonable (entries 3 and 4) to excellent yields (entries 1 and 2). Nonetheless, in cases where the heterocyclic ring was formed, such as in **3*β*e** and **3*β*f** (entries 5 and 6), the yields were rather low. Although it has recently been shown that $Co(PPh_3)_3Br$ was very active for cyclotrimerization of various alkynes and especially dipropargyl ether,[18b,20] the reaction of **1*β*** with **2a** and **2f** afforded the corresponding products **3*β*a** and **3*β*f** in only 23 and 25% yields (entry 5 and 6), respectively.

Next, we decided to carry out Ni-catalyzed cyclotrimerizations. In contrast to the previously used catalytic system ($NiBr_2$(dppe)/Zn), in this instance, we chose to use Ni(0)−phosphine complexes generated from $Ni(cod)_2$ and triphenylphosphine because of their known high catalytic activity.[21] However, the yields of cyclotrimerization products

Table 2. Cyclotrimerization of **1*β*** with **2** to **3*β*** Catalyzed by Various Catalysts[a]



entry	diyne **2**	catalyst	product **3*β***	yield (%)[b]
1	**2a**	$Rh(PPh_3)_3Cl$	**3*β*c**	95
		$Ni(cod)_2$/2PPh_3		74
		Cp*RuCl(cod)		95
		$Co(PPh_3)_3Br$		23
2	**2b**	$Rh(PPh_3)_3Cl$	**3*β*b**	81
		$Ni(cod)_2$/2PPh_3		76
		Cp*RuCl(cod)		40
3	**2c**	$Rh(PPh_3)_3Cl$	**3*β*c**	62
		$Ni(cod)_2$/2PPh_3		50
		Cp*RuCl(cod)		39
4	**2d**	$Rh(PPh_3)_3Cl$	**3*β*d**	52
		$Ni(cod)_2$/2PPh_3		42
		Cp*RuCl(cod)		33
5	**2e**	$Rh(PPh_3)_3Cl$	**3*β*e**	12
		$Ni(cod)_2$/2PPh_3		45
		Cp*RuCl(cod)		41
6	**2f**	$Rh(PPh_3)_3Cl$	**3*β*f**	32
		$Ni(cod)_2$/2PPh_3		30
		Cp*RuCl(cod)		30
		$Co(PPh_3)_3Br$		25

[a] The reaction was carried out at 20 °C. [b] Isolated yields.

3*β* (30−59%) were generally lower than those obtained with the Rh catalyst. Only in the case of the reaction with dipropargyltosylamide **2e** (entry 5) was the use of Ni catalysis advantageous: the yield of **3*β*e** (45%) was 3-fold higher than that obtained with the Rh catalyst (13%).

Interestingly, the use of Cp*RuCl(cod),[13,14,22,23] which has recently been used for a number of high-yielding cyclotrimerizations, did not meet our expectations. Generally, the yields of cyclotrimerized products **3*β*** (30−95%) were lowest in comparison with other catalysts. The only exception was the cyclotrimerization of **2a** with **1*β*** (entry 1), where the yield matched the one obtained with Wilkinson's catalyst. At the moment, we are not able to offer any sensible explanation as to why this otherwise highly active catalyst known for its tolerance to a wide array of functional groups gave these surprisingly inferior results.

In conclusion, we have shown that a transition metal complex catalyzed [2 + 2 + 2]-cyclotrimerization of α,ω-

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diynes with C-ethynyldeoxyriboside under simple and mild reaction conditions is an effective synthetic tool for preparation of anomerically pure C-aryldeoxyribosides. Although all Rh, Ru, and Ni complexes proved to be effective for catalyzing the reaction, the best results were obtained with the stable and easy to handle Wilkinson's catalysts ($Rh(PPh_3)_3Cl$). From a synthetic point of view, the advantage of this strategy is in the modular approach with regard to structural variety of the α,ω-diynes, the functional group compatibility of the transition metal catalysis with a wide variety of functional groups in the reactants, and an easily removable *p*-toluoyl protective group in the deoxyriboside. This approach will be further used in the synthesis of a large series of new C-nucleosides applicable in bioorganic and medicinal chemistry.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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