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Synthesis of *C*-arylglycosides *via* Ru(II)-catalyzed [2 + 2 + 2] cycloaddition

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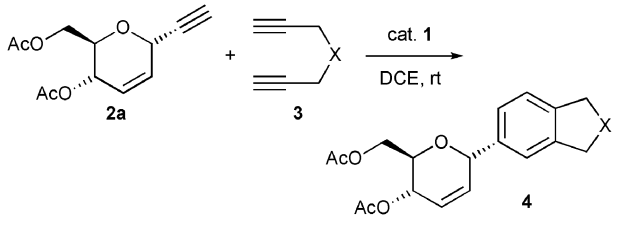
Received (in Cambridge, Uk) 28th July 2004, Accepted 22nd September 2004
First published as an Advance Article on the web 7th October 2004

In the presence of catalytic amounts of Cp*RuCl(cod), the cycloaddition of 1,6-diynes with various *C*-alkynylglycosides proceeded at ambient temperature to afford *C*-arylglycosides in 46–93% yields.

C-Glycosides, in which the glycosidic oxygen is replaced by a carbon atom, have attracted considerable attention in carbohydrate and biological chemistry, because of their stability toward the enzymatic and acidic hydrolysis. Frequently encountered *C*-glycoside motifs in nature are *C*-arylglycosides. Anthracyclinone *C*-glycosides are representative examples, exhibiting biological activities.[1] The construction of these natural *C*-arylglycosides have been an important subject in synthetic organic chemistry. *C*-Arylglycoside frameworks are generally obtained by the direct arylation of appropriate carbohydrate precursors.[2] However, the control of regiochemistry is a crucial problem when a highly substituted aromatic precursor is employed for this purpose. In this context, alternative methods have recently been developed by exploiting benzannulation and cycloaddition technologies.[3] The [2 + 2 + 2] cycloaddition of α,ω-diynes with *C*-alkynylglycosides is also a convergent and atom-economical approach. Although McDonald and co-workers have realized this method for the first time in the synthesis of anthraquinone *C*-glycosides,[4] the scope of the [2 + 2 + 2] cycloaddition route has remained largely unexplored. Here, we report on *C*-arylglycoside synthesis by means of the Ru(II)-catalysed cycloaddition.

At the outset, the D-glucal-derived *C*-alkynylglycoside **2a**[5] was subjected to the ruthenium-catalyzed cycloaddition with dimethyl dipropargylmalonate **3a** (Scheme 1). Our previously reported protocol,[6] however, gave rise to considerable amounts of the diyne dimer. In order to suppress this side reaction, a solution of **3a** in dry degassed 1,2-dichloroethane (DCE) was added to a DCE solution containing 5 mol% Cp*RuCl(cod) **1** (Cp* = η^5-C_5Me_5, cod = 1,5-cyclooctadiene) and 2 equiv. of **2a** over 2.5 h *via* syringe pump at ambient temperature, and the solution was further stirred for 24 h. Purification with silica gel chromatography afforded the desired *C*-arylglycoside **4aa** in 50% yield together with the recovered **3a** (40%) and **2a** (16%) (Table 1, run 1). The yield was successfully improved to 85% by adding a solution of **3a** and 2 equiv. of **2a** to the catalyst solution (run 2). The syringe pump addition over 5 h realized the highest yield of 93% (run 3).† With a reduced amount of **2a** (1.5 equiv), the reaction was not completed even after overnight stirring, and the yield was lowered to 62% (run 4).



Scheme 1

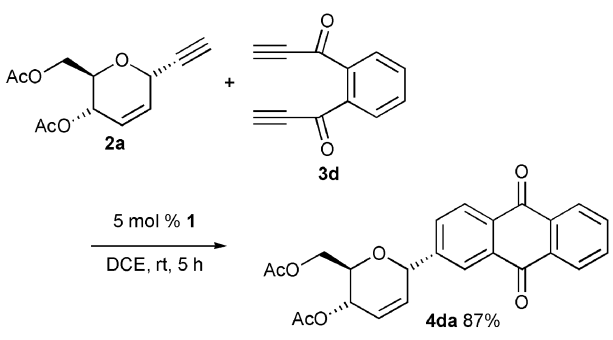
Table 1 Ru(II)-catalyzed cycloaddition of **2a** with **3**

Run	Diyne, X	Method[a]	**4** Yield	Recovered **2a**
1	**3a**, $C(CO_2Me)_2$	A	**4aa**, 50%[b]	16%
2	**3a**, $C(CO_2Me)_2$	B	**4aa**, 85%	49%
3	**3a**, $C(CO_2Me)_2$	C	**4aa**, 93%	32%
4	**3a**, $C(CO_2Me)_2$	D	**4aa**, 62%[b]	50%
5	**3b**, NTs	C	**4ba**, 89%	34%
6	**3c**, O	C	**4ca**, 46%	40%

[a] A: To a solution of 5 mol% **1** and **2a** (2 equiv.) was added a solution of **3** over 2.5 h, and the solution was stirred at rt for 24 h. B: To a solution of 5 mol% **1** was added a solution of **3** and **2a** (2 equiv.) over 2.5 h, and the solution was stirred at rt for 1.5 h. C: To a solution of 5 mol% **1** (10 mol% for run 6) was added a solution of **3** and **2a** (2 equiv.) over 5 h (10 h for run 6). D: To a solution of 5 mol% **1** was added a solution of **3** and **2a** (1.5 equiv.) over 5 h at rt, and the solution was stirred overnight. [b] The diyne **3a** was recovered in 40% (run 1) and 30% (run 4).

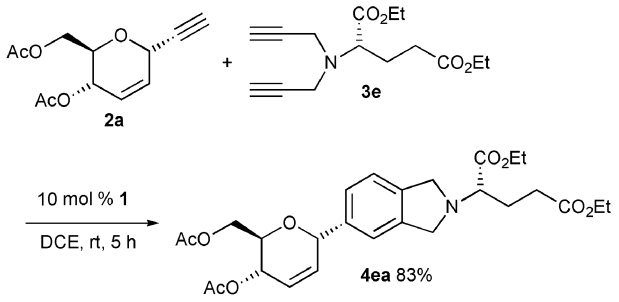
Under the optimal reaction conditions, the generality of the present protocol was examined with respect to the diyne substrate. The tosylamide derivative **3b** was allowed to react with **2a** in the same manner as with **3a** to afford **4ba** in 89% yield (Table 1, run 5). On the other hand, the less reactive propargyl ether **3c** required an increased catalyst loading of 10 mol% as well as the longer dropping time of 10 h (run 6). The desired product **4ca** was obtained in 46% yield. In addition to these 1,6-diynes, a 1,7-diyne, diketodiyne **3d**, could be used for the Ru(II)-catalyzed cycloaddition.[7] The reaction of **3d** with **2a** also proceeded at ambient temperature to furnish an anthraquinone *C*-glycoside **4da** in 87% yield (Scheme 2). The Ru(II) catalyst has a wide functional compatibility.[6] The *N*-propargylated glutamic acid derivative **3e** was allowed to react with **2a** without difficulty to obtain **4ed** in 83% yield (Scheme 3). This example is interesting as a novel and straightforward strategy to synthesize amino acid–sugar conjugate molecules, which are important structural motifs in glycopeptides.[8]

We have reported that the Cp*RuCl-catalyzed [2 + 2 + 2] cycloaddition of unsymmetrical diyne bearing a terminal substituent with terminal monoalkynes selectively gave *meta*-substituted benzenes.[6] Taking advantage of this selectivity, a bicyclic

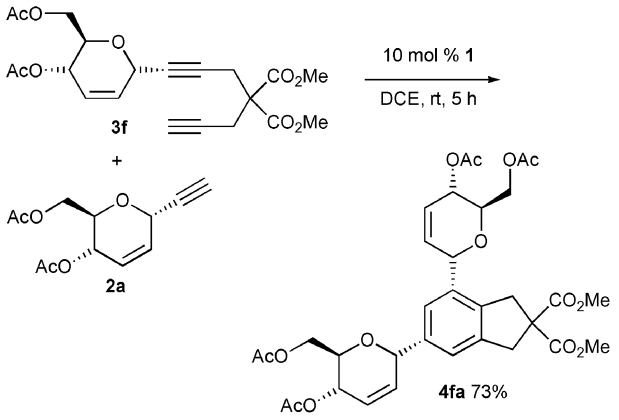


Scheme 2

DOI: 10.1039/b411442f



Scheme 3



Scheme 4

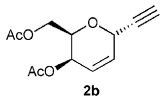
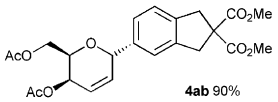
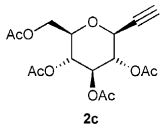
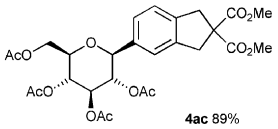
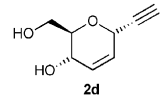
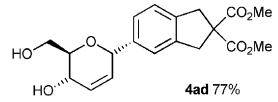
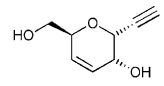
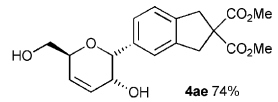
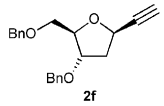
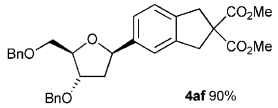
benzene possessing two *C*-glycosyl groups, which are placed in mutually *meta*-positions, might be synthesized from a *C*-diynylglycoside such as **3f**. Such a bis *C*-arylglycoside motif has been an attractive target, since it is found in naturally occurring antibiotic kidamycin and its analogues.[9] Indeed, **4fa** was obtained in 73% yield as a single regioisomer from the diyne **3f** and **2a** (Scheme 4).

The Ru(II)-catalyzed *C*-arylglycoside formation also proved to be applicable to various types of *C*-alkynylglycosides (Table 2). The reaction of the malonate-derived diyne **3a** with the *C*-alkynylglycoside **2b** prepared from D-galactal gave the corresponding *C*-arylglycoside **4ab** in 90% yield. In addition to the unsaturated carbohydrate precursors **2a, b**, the D-glucose derivative **2c**[10] also gave , **4ac** in 89% yield. More significantly, the ruthenium catalysis tolerates hydroxy groups well. Thus, the unprotected carbohydrates **2d** and **2e**[11] were allowed to react with **3a** under the same reaction conditions to afford **4ad** and **4ae** in 77 and 74% yields, respectively. Finally, the deoxy-D-ribose derivative **2f**[12] was examined as an alkynylated furanose. The expected **4af** was isolated in 90% yield.

In conclusion, we successfully developed the general protocol to constract *C*-arylglycosides by means of the Ru(II)-catalyzed [2 + 2 + 2] cycloaddition of α,ω-diynes with *C*-alkynylglycosides under mild reaction conditions.

We gratefully acknowledge financial support from the Naito Research Grant.

Table 2 Synthesis of *C*-aryglycosides **4ab–4af** from *C*-alkynylglycosides **2b–2f** and diyne **3a**[a]

C-Alkynylglycosides	*C*-Arylglycosides
 **2b**	 **4ab** 90%
 **2c**	 **4ac** 89%
 **2d**	 **4ad** 77%
 **2e**	 **4ae** 74%
 **2f**	 **4af** 90%

[a] To a solution of 5 mol% **1** was added a solution of **3a** and **2** (2 equiv.) over 5 h *via* syringe pump at room temperature.

Notes and references

† *Typical procedure–Synthesis of* **4aa**: To a solution of Cp*RuCl(cod) **1** (5.7 mg, 0.015 mmol) in dry degassed 1,2-dichloroethane (1 mL) was added a solution of **3a** (67.4 mg, 0.32 mmol) and **2a** (143.0 mg, 0.6 mmol) in 1, 2-dichloroethane (4 mL) over 5 h *via* syringe pump at room temperature. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column flush chromatography (eluent: hexane : AcOEt = 6 : 1) to afford **4aa** (132.8 mg, 93%) as colorless solids.

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