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Efficient Grignard-type addition of sugar alkynes via C–H activation to imines using Cu–Ru catalyst under microwave conditions

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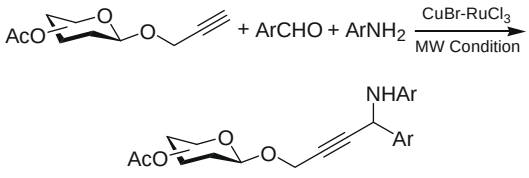
ABSTRACT

Very productive Grignard-type addition of sugar alkynes to imines via C–H activation using Cu–Ru catalyst was achieved under microwave conditions. The resulting glyco-conjugates are attractive for future evaluation as potential drug-like molecules.

Recent development of glycomics has earned a great deal of interest toward synthetic glyco-conjugates for future drug design and development.[1–5] Therefore, conjugation of sugars with various aglycons has become a challenge for the synthetic carbohydrate chemists in recent years.[6–11] Owing to the ease of performance, multicomponent reactions (MCRs) are growing in popularity for the generation of highly complex and medicinally relevant compound libraries.[12] One such approach is the so-called A^3-coupling, involving alkyne, aldehyde, and amine.[13–20] This is of particular interest because of the three-point diversity to construct a relevant library where sugar alkynes can be used to generate the corresponding sugar propargyl amine derivatives. These propargyl amines are attractive targets for their functional decoration and further derivatization is possible by using the internal alkyne moiety. Recent literature reports revealed metal-catalyzed Grignard-type C–H activation as a powerful tool for the generation of propargyl amines via coupling of alkynes with imines.[21] Here, we report an efficient synthesis of the sugar propargyl amines via Cu–Ru catalyzed C–H activation under micowave conditions using propargyl glycosides and different aldehydes and amines (Scheme 1).

Our experiment started with the reaction of the acetylated propargyl glucoside **1** with the imine generated in situ by the coupling between benzaldehyde and aniline. Using CuBr (30 mol %) as the sole catalyst at 80 °C in CH_3CN, the corresponding propargyl amine was obtained in 55% yield. Other Cu(I) salts except CuI (45% yield) failed to produce the desired derivative reasonably in the same condition. Use of AgBr produced the desired compound in 45% yields, whereas the use of AuI failed to form the propargyl amine derivative. To improve the yield further, we used 30 mol % CuBr in conjunction with 3 mol % $RuCl_3$ and the yield went up to 75% at 80 °C for 16 h. Concerned about the long heating time, we opted for microwave[22,23] and to our satisfaction, when the reaction was carried out with the same catalyst combination but at 130 °C for 35 min under microwave, 95% yield of the desired derivative was obtained. Even the reaction afforded 87% yield under solvent-free condition. It is worth noting that $RuCl_3$ alone failed to catalyze the transformation (Table 1).

Once settled on the catalyst combination and the reaction conditions, we focused our attention to explore the generality of the



Scheme 1. Cu–Ru catalyzed A^3-coupling between propargyl glycoside, aldehyde, and amine.

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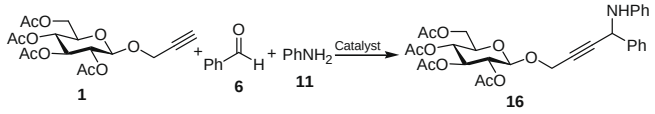
Table 1
Standardization of MCR between propargyl glucoside, benzaldehyde, and aniline using different catalysts and conditions[a]



No	Catalyst (mol %)	Conditions	Yield
1	CuBr (30)	MeCN, 80 °C, 16 h	55
2	CuCl (30)	MeCN, 80 °C, 16 h	35
3	$CuCl_2$ (30)	MeCN, 80 °C, 16 h	15
4	CuI (30)	MeCN, 80 °C, 16 h	45
5	$CuSO_4$ (30)	MeCN, 80 °C, 16 h	—
6	CuCN (30)	MeCN, 80 °C, 16 h	10
7	$Cu(OAc)_2$ (30)	MeCN, 80 °C, 16 h	—
8	$RuCl_3$ (3)	MeCN, 80 °C, 16 h	—
9	AgBr (30)	MeCN, 80 °C, 16 h	45
10	AuI (30)	MeCN, 80 °C, 16 h	—
11	CuBr (30)–$RuCl_3$ (3)	MeCN, 80 °C, 16 h	75
12	CuBr (30)–$RuCl_3$ (3)	MW, 130 °C, 5 min, MeCN	30
13	CuBr (30)–$RuCl_3$ (3)	MW, 130 °C, 20 min, MeCN	54
14	CuBr (30)–$RuCl_3$ (3)	MW, 130 °C, 35 min, MeCN	95
15	CuBr (30)–$RuCl_3$ (3)	MW, 130 °C, 35 min, neat	87

[a] The reactions were performed with 1.1 equiv of propargyl glucoside, 1 equiv of benzaldehyde, and 1.1 equiv of aniline.

procedure toward all the three variables; that is, propargyl glycoside, aldehyde, and amine. Therefore, propargyl glycosides of different sugars, different aldehydes and anilines were subjected in various combinations. Excellent yields were obtained in each case as summarized in Table 2. It is worth noting that when aliphatic amines and/or aliphatic aldehydes were used, no significant products were isolated from the complex mixture (Table 2, entries 12–14). Even aliphatic aldehydes, devoid of any α-hydrogen, failed to produce the desired product (Table 2, entries 13 and 14).

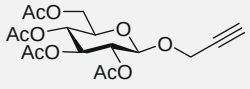
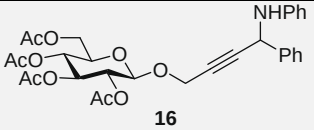
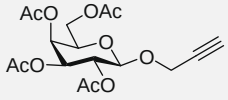
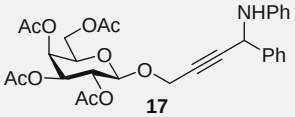
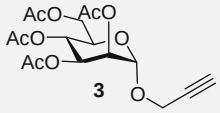
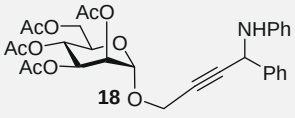
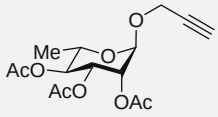
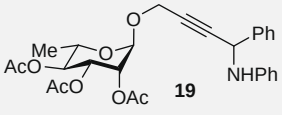
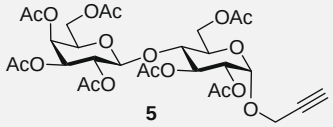
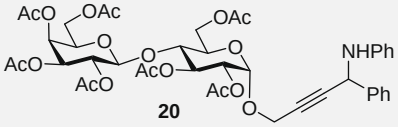
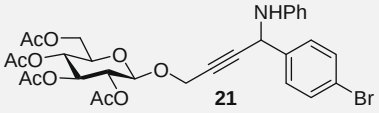
It is important to note that in a greener approach, we tried to do the reaction in an aqueous medium by using un-protected propargyl glycosides. Unfortunately, no significant product could be isolated from the reaction mixture. May be this is due to the poor solubility of propargyl glycosides in water and also the presence of several interactive –OH groups.

A tentative mechanism has been proposed which involves the activation of the C–H bond of sugar alkyne by a Ru(II) species[24] which was possibly generated in situ from the reduction of Ru(III) by sugar alkyne and also activation of imine with copper. The ruthenium intermediate thus generated then reacts immediately via Grignard-type addition with the activated imine to afford the corresponding nucleophilic addition product and the copper and ruthenium salts were released for further reaction (Scheme 2).

In conclusion, we have developed an efficient protocol for the synthesis of glycosyl propargyl amines through A^3-coupling of propargyl glycosides, aldehydes, and amines under microwave conditions. The procedure was proved to be general for different synthons. The library of compounds thus synthesized will be evaluated for appropriate medicinal activities and the results will be published in due course.

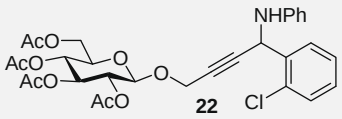
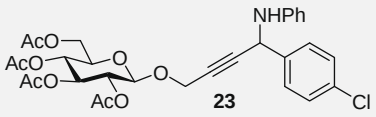
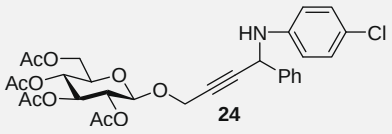
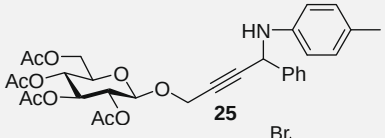
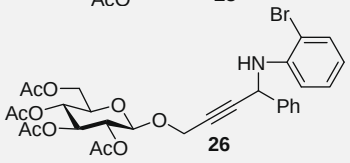
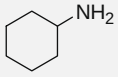
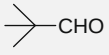
A typical procedure for the A^3-coupling reaction is as follows: A mixture of aldehyde (1 mmol) and amine (1.1 mmol) was stirred at 60 °C for 1 h. Then propargyl glycoside (1.1 mmol) in CH_3CN (2 mL) was added followed by CuBr (30 mol %) and $RuCl_3$ (3 mol %). After sealing the microwave vial, it was placed in the reactor (Biotage, Initiator 1™) and the reaction was carried out at 130 °C for 35 min. After completion of the reaction, the mixture was diluted

Table 2
Synthesis of glycosylated propargyl amines via Cu–Ru catalyzed Grignard-type C–H bond activation under microwave condition

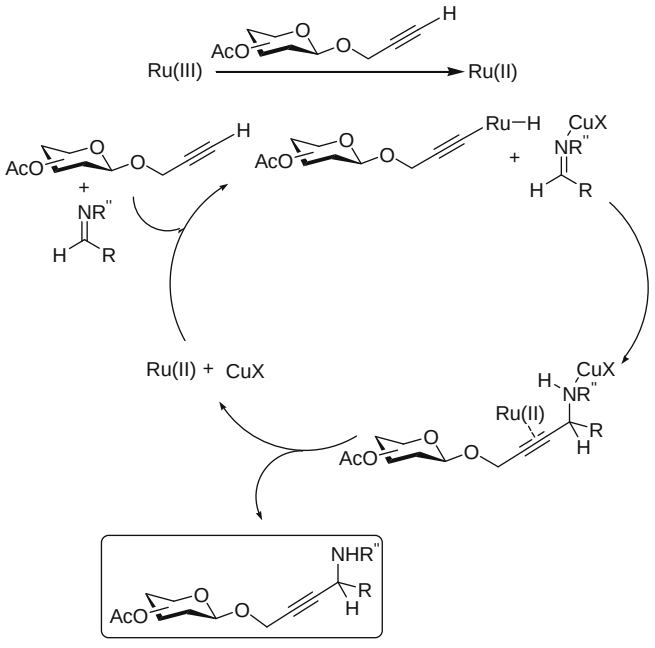
Entry	Propargyl glycoside	Aldehyde	Aniline	Product	Yield[a] (%)
1	 **1**	C_6H_5CHO (**6**)	$C_6H_5NH_2$ (**11**)	 **16**	95
2	 **2**	**6**	**11**	 **17**	90
3	 **3**	**6**	**11**	 **18**	83
4	 **4**	**6**	**11**	 **19**	95
5	 **5**	**6**	**11**	 **20**	80
6	**1**	**6**	*p*-Br–C_6H_4–CHO (**12**)	 **21**	92

(*continued on next page*)

Table 2 (*continued*)

Entry	Propargyl glycoside	Aldehyde	Aniline	Product	Yield[a] (%)
7	**1**	**6**	*o*-Cl–C_6H_4–CHO (**13**)	 **22**	89
8	**1**	**6**	*p*-Cl–C_6H_4–CHO (**14**)	 **23**	96
9	**1**	*p*-Cl–C_6H_4–NH_2 (**7**)	**11**	 **24**	85
10	**1**	*p*-Me–C_6H_4–NH_2 (**8**)	**11**	 **25**	87
11	**1**	*o*-Br–C_6H_4–NH_2 (**9**)	**11**	 **26**	88
12	**1**	 **10**	**11**		–
13	**1**	**6**	 **15**		–
14	**1**	**10**	**15**		–

[a] Yields reported are those obtained after chromatographic purification.



Scheme 2. Proposed pathway for imine addition via C–H activation.

with CH_2Cl_2 (15 mL) and washed with H_2O (2 × 15 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated in vacuo. The residue thus obtained was purified through flash chromatography using *n*-hexane–EtOAc (3:1) as solvent.

Acknowledgments

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Supplementary data

Supplementary data (detailed analytical data and copies of ^1H and ^{13}C NMR spectra of all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.005.

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