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ARTICLE TYPE

Zinc mediated activation of terminal alkynes: stereoselective synthesis of alkynyl glycosides.

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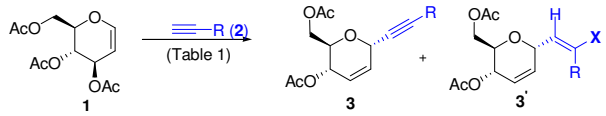
Zinc mediated alkynylation reaction was studied for the preparation of *C*-glycosides from unactivated alkynes. Different glycosyl donors such as glycals and anomeric acetates were tested towards alkynyl zinc reagent obtained from alkynes using zinc dust and ethyl bromoacetate as an additive. The method provides a simple, mild and stereoselective access of alkynyl glycosides both from aromatic and aliphatic acetylenes.

Chiral building block synthesis from cheap and easily available starting materials has always remained a thrust in organic chemistry.[1] In this endeavour carbohydrate have un interruptedly maintained a prominent place. Though these naturally occurring materials on their own serve as starting materials for chiral synthesis [2] but attachment of extra carbon chain gives rise to new chiral scaffolds of synthetic and biological importance.[3] In this regard, alkynyl *C*-glycosides have attracted tremendous interest due to the presence of a multiple bond; a real asset for target oriented synthesis and diversity creation.[4] With our continuing interest in this direction,[5] we have reported direct access of alkynyl *C*-glycosides from unactivated aromatic alkynes under coppertriflate/ascorbic acid catalysis.[5a] Despite several advantages over the literature methods,[6] the main demerit of our reagent system lay in its inefficiency to activate aliphatic alkynes and glycosyl donors other than glycals. In order to overcome these shortcomings of our strategy, we continued our studies in develop a universal reagent for *C*-alkynylation of glycals and other carbohydrate donors.

C-C bond formation reactions using *in situ* generated organo-zinc species have been thoroughly investigated in unsaturated systems.[7] Low reactivity and broad functional group compatibilities of these organo-metallic species have widened their applications in synthetic organic chemistry.[7] In carbohydrate chemistry, however, the use of organo-zinc reagents is limited due to solubility problem such as use of combination of solvents,[8] use of strong base,[9] poor anomeric selectivity,[10] oxidation-reduction sequence,[11] excess use of promoters and drastic reaction condition.[8] To the best of our understanding, there are no reports of applications of organo-zinc reagents for *C*-alkynylation of glycals and other glycosyl donors. In this letter, we would like to disclose our findings regarding *C*-alkynylation in carbohydrates with high stereocontrol obviating the use of strong Lewis acids or bases and exploiting both aromatic and aliphatic alkynes.

In order to develop a reagent system for *C*-alkynylation of glycals from unactivated aliphatic alkynes, 3,4,6- tri-*O*-acetyl-D-glucal (**1**) and 1-octyne (**2**) were allowed to react in the presence of various Lewis acids and metals, results of which is summarized in table 1. Initially we attempted Lewis acids like Zn & In halides (table1, entries 1-3) where we observed the formation of alkynl glycoside **3** and halogenated vinyl glycoside **3'** in equal amounts. Changing the metal halide with iron chloride failed to give the desired product **3**, instead we obtained complex mixtures of halogenated vinyl glycoside **3'**(table1, entry 4).

Table 1. Standardisation of reaction conditions for *C*-alkynylation.



Entry	Reagent[a]	Solvent/T (°C)	Time (h)	Yield[b] (%)(**3:3'**)
1	$ZnBr_2$ (0.2eq)	DCM/ rt to 40	5h	72 (1:1)
2	$ZnCl_2$ (0.2eq)	DCM/ rt to 40	5h	70 (1:1)
3	$InCl_3$ (0.2eq)	DCM/ rt to 40	3h	40 (1:1)
4	$FeCl_3$ (0.2eq)	DCM/ rt to 40	6h	46 (0:1)[c]
5	$Fe(OTf)_3$ (0.2eq)	DCE/0 to RT	16h	20 (1:0)
6	$In(OTf)_3$ (0.2eq)	DCE/0 to RT	16h	20 (1:0)
7	TMSOTf (0.2eq)	DCE/0 to RT	16h	18 (1:0)
8	Zn (1.5eq)	DCM/40	24h	NR
9	**Zn(1.5eq)/A[d]**	**DCM/40**	**6h**	**68 (1:0)**
10	Zn(1.5eq)/A	THF/40	12h	NR
11	In(1.5eq)/A	DCM/40	12h	34 (1:0)
12	Zn(1.5eq)/B[e]	DCM/40	12h	NR

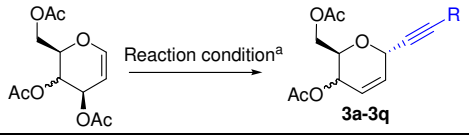
[a] In all cases 0.5 mmol of **1**, 0.75 mmol. of (1-octyne) **2**. [b] Combined yield of isolated products (**3**, **3'**) obtained after column chromatography. [c] A combined yield of complex mixture. [d] A = $BrCH_2COOC_2H_5$ (1eq). [e] B = CH_3I (1eq).

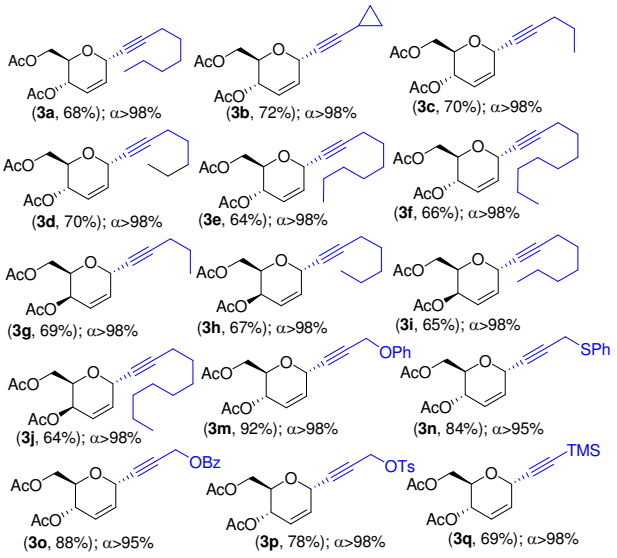
Triflates such as $Fe(OTf)_3$, $In(OTf)_3$, TMSOTf (table 1, entry 5-7) furnished the desired product **3** exclusively albeit in poor yield (18-20%). Taking cue from the literature reports for zinc mediated alkyne activation [12] when the above reaction was carried

out using zinc powder in absence of any additive, the starting material was recovered as such (table 1, entry 8). We observed that the choice of additive and nature of the solvent play a big role in the outcome of the reaction. After extensive investigation of additives and solvents, it was heartening to witness the formation of desired *C*-alkynyl glycoside (**3**) (68%) with zinc powder in the presence of ethyl bromoacetate as an additive in DCM at 40 °C (table1, entry 9). Other solvents like THF (table 1, entry 10) or other additives like methyl iodide (table1, entry 12) failed to give the desired product. Replacing zinc with indium produced the desired product in lower yield (table1, entry 11).

With the optimized reaction conditions at our disposal, a series of aliphatic *C*-alkynes with different chain length and additional functionality were allowed to react with glycals and the results are summarized in scheme 1. All the alkynes reacted smoothly to yield the desired product in moderate to good yield with high stereo selectivity.

Scheme 1.Scope of reaction with aliphatic alkynes

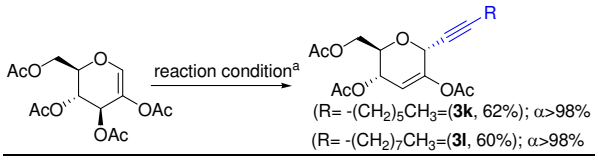




[a] Conditions: bromoethylacetate (1.0 eq.), alkyne (1.5 eq.), zinc dust (1.5 eq.), CH_2Cl_2 (3 mL), 40 °C, 1h, then glycal (1.0 eq.), 40 °C, 6-8 h.

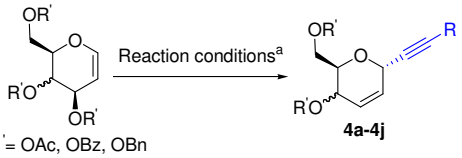
Glucal (**3a-3f**), galactal (**3g-3j** substrates (scheme 2) afforded *C*-glycosides with high selectivity. In addition to these, reaction of terminal alkynes containing *O*- and *S*- substituent (**3m, 3n**), including ester (**3o**), tosylate (**3p**) yielded the desired product expanding the scope of the reacting partners. One of the key features of this methodology is its mildness as evident from the reaction of TMS acetylene under similar condition leading to the formation of alkynylated glycoside (**3q**) retaining the sillyl protection at the terminal position which is otherwise not possible.

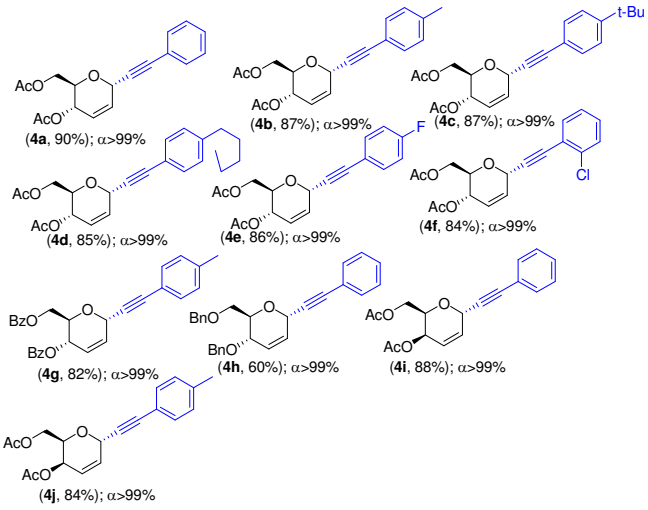
Scheme 2. Reaction scope with 2-acetoxy glucal



Similarly, in case of 2-acetoxy D-glucals we were delighted to obtain 2-acetoxy glycosides containing enol ester moiety whereas 2-keto glycosides are the major product with other Lewis acids under harsh condition.[4a] After getting encouraging result with aliphatic acetylenes we tried to make this protocol more general by studying its applications to aromatic alkynes. As anticipated aromatic alkynes gave much higher yields as compared to aliphatic ones and the results are depicted in Scheme 3. Glycals bearing, ester (**4a**-**4j**) and ether (**4h**) protecting groups reacted smoothly with a range of aryl acetylenes carrying electron donating or withdrawing groups to give the corresponding alkynyl *C*-pseudo glycals in good to excellent yields comparable with TMSOTf condition or superior to copper triflates/ascorbic acid condition.[5a]

Scheme 3. Substrate scope of reaction towards aromatic alkynes.

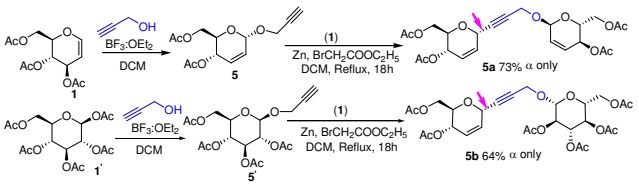




[a] Bromoethylacetate (1.0 equiv.), alkyne (1.5 equiv.), zinc dust (1.5 equiv.), CH_2Cl_2 (3 mL), 40 °C, 1h, then glycal (1.0 equiv.), 40 °C, 4-5 h.

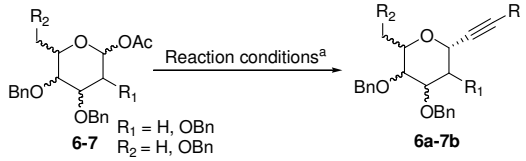
To demonstrate the versatility of the reagent system, pseudo-disaccharides **5a**, **5b** were prepared (Scheme 4). Thus, treatment of propargyloxy-glycoside **5**, **5'** derived from D-glucal (**1**) or glucose penta-acetate (**1'**) with tri-*O*-acetyl-D-glucal under optimized condition led to the formation of disaccharides in moderate yields

Scheme 4. Synthesis of pseudo-disaccharides.

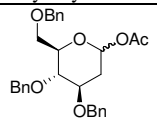
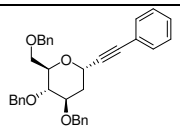
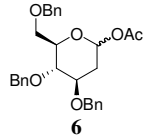
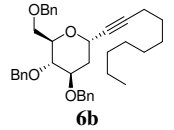
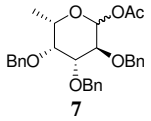
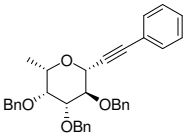
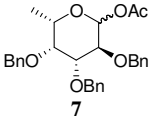
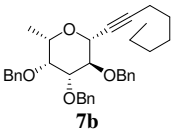


Further extension of this strategy, other glycosyl donors like anomeric acetates were allowed to react with alkynes under optimized reaction condition. To our satisfaction, all the donors reacted with both aliphatic and aromatic alkyne partners to afford the corresponding glycosides (**6a,6b;7a,7b**) in good to excellent yield with high stereoselectivity and the results are represented in table 2. However, in this case of peracetylated glucose we failed to observe any *C*-glycosylated product even after 48 h.

Table 2. Direct *C*-glycosylation of unactivated alkynes with glycosyl acetates



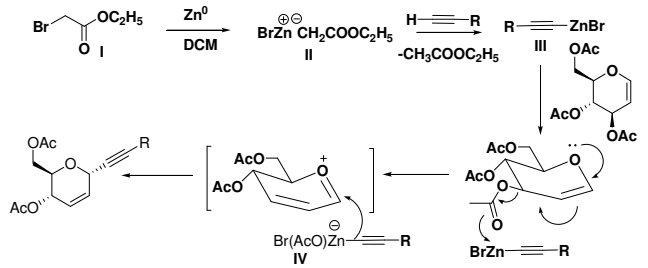
6-7 6a-7b

Entry	Glycosylacetate	Product	Yield(%)
1	 **6**	 **6a**	64
2	 **6**	 **6b**	60
3	 **7**	 **7a**	60
4	 **7**	 **7b**	58

[a] Bromoethylacetate (1.0 equiv.), alkyne (1.5 equiv.), zinc dust (1.5 equiv), CH_2Cl_2 (3 mL), 40 °C, 1-2 h, then Glycosyl acetate (1.0 equiv.), 40 °C, 24 h.

In order to explain the alkyne activation under the standardised conditions a plausible reaction mechanism is outlined in Scheme 5. Formation of organo-zinc compound (**II**) from α-halogenester (**I**) and zinc metal is well known.[7c,12] Exchange of sp-proton from terminal alkynes to organo-zinc species (**II**) leads to the formation of zinc acetylide (**III**) with the removal of ethyl acetate. Subsequently, the zinc acetylide reacts with glycal via an allylic oxocarbonium intermediate and a zincate complex (**IV**) at C-1 from the α-side, to afford the desired *C*-glycoside with α-selectivity. Isobe[6d,13] explained the α selectivity in the case of alkynylation with trimethyl acetylenes, by electronic effects on the oxocarbenium intermediates involved in the transformation. In case of anomeric acetates the reaction mechanism proceeds through oxocarbonium intermediate resulting from the expulsion of anomeric acetate.[6e]

Scheme 5. Plausible mechanism of C-alkynylation.



In conclusion, we have developed a new and very mild zinc-mediated method for the stereoselective introduction of an unactivated alkynyl group to glycals, and glycosyl acetates. This offers a convenient access to *C*-glycosides with good yields and has broad substrate scope.

Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures and compound characterization data is given.

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