SILVER SALT-MEDIATED BENZYLATION OF CARBOHYDRATES UNDER MILDLY ACIDIC CONDITIONS

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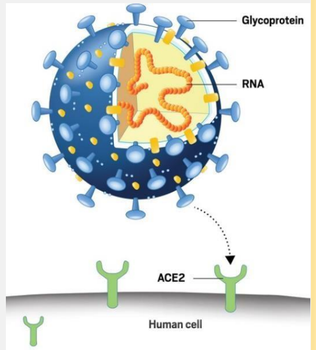
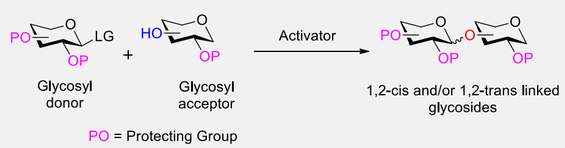
CARBOHYDRATES

- Carbohydrates represent a large group of macromolecules that play many important roles in the body.
- Carbohydrates provide an energy supply for organisms, but they are also involved in a myriad of other processes and every major disease.
- For example, severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), uses its spike glycoprotein to bind to receptors and mediate virus entry.
- No effective treatments for the associated disease COVID-19 have been discovered, but understanding how SARS-CoV-2 enters cell provides information for drug design.
- Chemical synthesis of carbohydrates leads to advancements in chemistry and paths the way towards carbohydrate-based drug discovery.

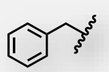


OLIGOSACCHARIDE ASSEMBLY

- The key aspect for oligosaccharides assembly is the attachment of various monosaccharaides unties via glycosidic bond.
- The linkage is constructed by a chemical glycosylation reaction whereas a nucleophilic displacement of a leaving group (LG) of the glycosyl donor with a hydroxyl moiety of the glycosyl acceptor in the presence of an activator employed.



- The sequencing of oligosaccharides require functional groups to be temporarily blocked by protecting groups.
- Using benzyl ethers as protecting groups for hydroxyls is a standard way of obtaining efficient building blocks in carbohydrate chemistry.
- Benzyl groups show stability, easy installation, and compatibility with many reaction conditions.



CURRENT METHOD ISSUES

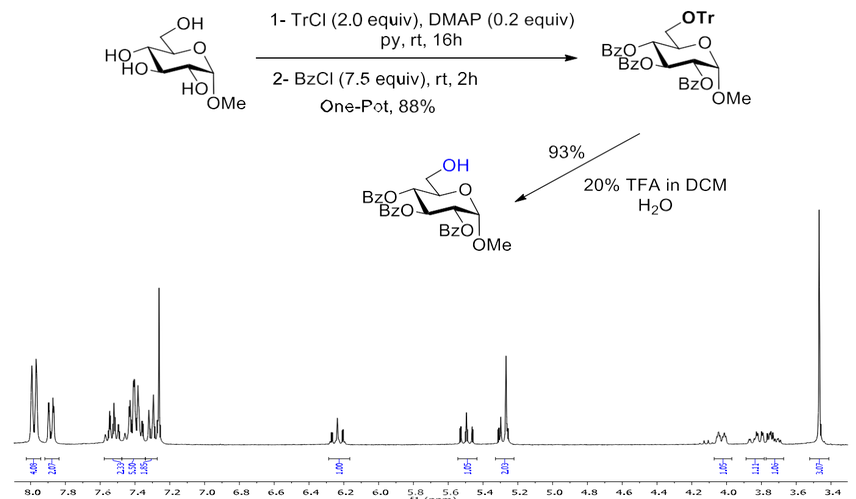
- Uniform benzylation of carbohydrates can be efficiently achieved, but it typically requires excess reagents and/or harsh reaction conditions.
- There are 2 current methods that are the most common for selective benzylation of carbohydrates.

NaH	Ag_2O
• Low yield in presence of base-labile protecting groups • NaH waste	• Excess use of reagents • Fresh Ag_2O need to be used • Low yield • Long reaction time

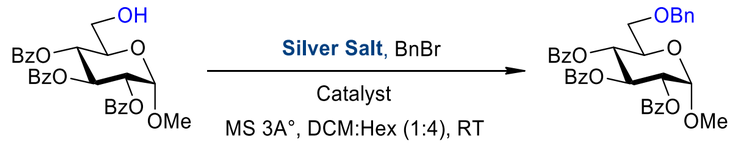
PROPOSED RESEARCH TOPIC

- Herein, we report the investigation of a new benzylation reaction that makes use of mildly acidic conditions.
- The main focus of this study is to identify suitable silver salts that would provide high regioselectivity, excellent yields, and help minimize side reactions.

SYNTHESIS OF MAIN SUBSTRATE



SILVER SALT INVESTIGATION



Entry	BnBr (equiv)	Ag_2SO_4 (equiv)	TMSOTf (equiv)	Time / Yield (%)
1	2.0	0.6	1.0	24h / 5

Entry	BnBr (equiv)	AgCN (equiv)	TMSOTf (equiv)	Time / Yield (%)
1	2.0	2.0	1.0	16h / 24

Entry	BnBr (equiv)	$AgClO_4$ (equiv)	TMSOTf (equiv)	Time / Yield (%)
1	2.0	2.0	1.0	16h / 50

Entry	BnBr (equiv)	AgOBz (equiv)	TMSOTf (equiv)	TfOH (equiv)	Time / Yield (%)
1	2.0	2.0	1.0	-	16h / 35
2	1.5	2.0	1.0	-	16h / 58
3	1.2	2.0	1.0	-	16h / 54
4	1.2	2.0	2.0	-	16h / 20
5	1.2	2.0	-	1.0	16h / 48

Entry	BnBr (equiv)	AgOAc (equiv)	TMSOTf (equiv)	Time / Yield (%)
1	1.5	2.0	1.0	16h / 53
2	1.2	2.0	1.0	16h / 60
3	1.2	2.0	2.0	16h / 80

CONCLUSIONS

- Synthesis of the main investigated substrate have been performed.
- Different silver salts have been investigated under TMSOTf and TfOH catalysts.
- AgOAc-TMSOTf combination system was the most promising with 80% product formation.
- Different substrates will be investigated under the devoted condition.
- New solvents and solvent systems can be investigated.

REFERENCES

(1) Ou, X.; Liu, Y.; Lei, X.; Li, P.; Mi, D.; Ren, L.; Guo, L.; Guo, R.; Chen, T.; Hu, J.; Xiang, Z.; Mu, Z.; Chen, X.; Chen, J.; Hu, K.; Jin, Q.; Wang, J.; Qian, Z. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat. Commun.* **2020**, *11*, 1620.

(2) Wang, T.; Demchenko, A. V. Synthesis of carbohydrate building blocks via regioselective uniform protection/deprotection strategies. *Org. Biomol. Chem.* **2019**, *17*, 4934-4950.

(3) Cao, Y.; Okada, Y.; Yamada, H. Facile and regioselective preparation of partly O-benzylated D-glucopyranose acetates via acid-mediated simultaneous debenzylation-acetolysis. *Carbohydr. Res.* **2006**, *341*, 2219-2223.

(4) Malik, S.; Dixit, V. A.; Bharatam, P. V.; Kartha, K. P. A simple, mild, and regioselective method for the benzylation of carbohydrate derivatives promoted by silver carbonate. *Carbohydr. Res.* **2010**, *345*, 559-564.