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One-Pot Oligosaccharide Synthesis Exploiting Solvent Reactivity Effects

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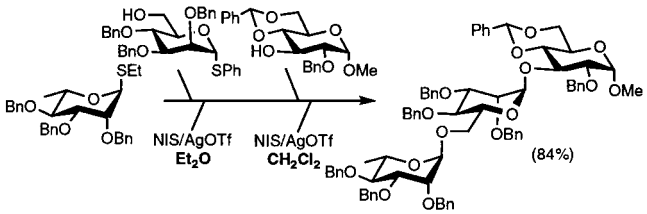
ABSTRACT



One-pot syntheses of trisaccharides have been accomplished simply by changing the solvent system between the two subsequent glycosylation reactions and utilizing the difference in glycosylation rate between different solvents. By tuning the reactivity of acceptors and donors and performing the first glycosylation in Et_2O (low glycosylation rate) and the second in CH_2Cl_2/Et_2O (higher glycosylation rate), trisaccharides were synthesized in high yields (76–84%).

Orthogonal glycosylations and one-pot synthesis of oligosaccharides have recently been made possible with the development of new types of glycosyl donors, especially thioglycosides[1] and *n*-pentenyl[2] glycosides. Various approaches to accomplishing such glycosylations have been used, utilizing the reactivity diversity of, e.g., various types of glycosyl donors,[3] differently protected glycosyl donors,[4] or thioglycoside donors with different thiol aglycons.[5] Solvent effects have been used to influence the stereoselectivity in glycosylation using nonparticipating protecting groups, e.g., diethyl ether or dioxane/toluene to promote the formation of the α-product[6] and CH_3CN the β-product.[7] However, the solvent also affects the rate of the glycosylation. Here we show that one-pot trisaccharide synthesis is made possible just by changing the solvent used for the glycosylation reaction.

Glycosylations are frequently carried out in CH_2Cl_2 because the rate of glycosylation is usually high in this solvent. Changing to another solvent, e.g., diethyl ether or (even more pronounced) CH_3CN, generally slows down the reaction rate. We reasoned that this solvent rate effect might be large enough to benefit one-pot oligosaccharide synthesis. The first donor was designed so that it could be activated in most solvents to form a disaccharide. This disaccharide acted then as a less reactive second donor, which was only activated in certain solvents to give a trisaccharide. In this manner one-pot trisaccharide syntheses should be feasible simply by changing the solvent between the two coupling steps. This concept is proven in a number of model studies (Schemes 1 and 2).

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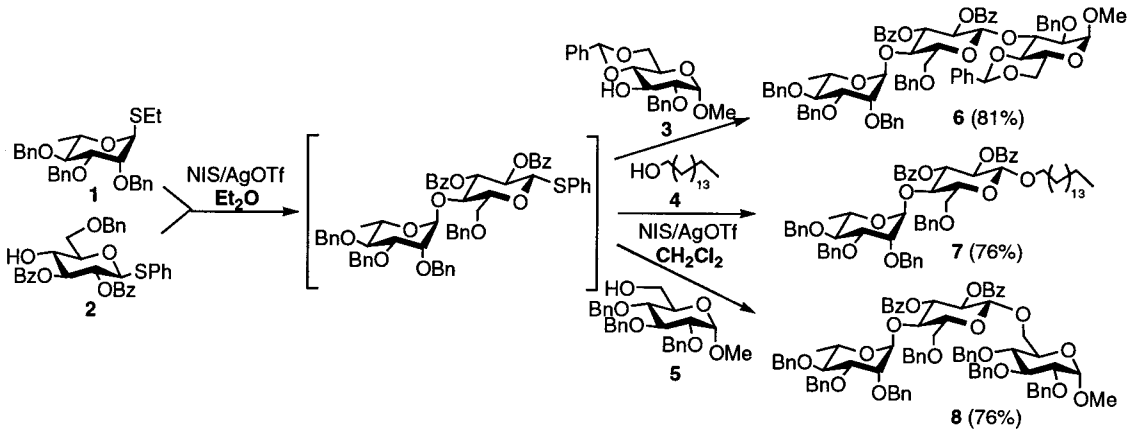
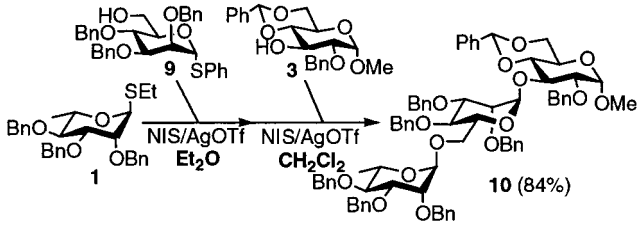
Scheme 1



All donors used were thioglycosides. As the more reactive donor, the perbenzylated ethyl thioglycoside **1** of L-rhamnose was chosen. As the first acceptors, a thiophenyl glucoside with a 2-*O*-participating group (**2**) and a thiophenyl mannoside with a 2-*O*-nonparticipating group (**9**) were selected, and as the second acceptor, compounds **3**, **4**, and **5** were chosen. When donor **1** and any of the thiophenyl glycosides **2** and **9** were dissolved in diethyl ether and the promoter, NIS/AgOTf, was added, only **1** was activated to give the corresponding thiophenyl disaccharides in almost quantitative yield according to TLC. Simply by adding the last acceptor, i.e., **3**, **4**, or **5**, and additional promoter *dissolved in* CH_2Cl_2, were the intermediate thiophenyl disaccharide donors activated to give the trisaccharide products **6**, **7**, **8**, and **10** in high yields[8] and with stereospecificity.[9] If the first reaction was carried out in CH_2Cl_2, a complex product mixture was obtained. If the latter addition was performed using diethyl ether as solvent, no further reaction took place.

Scheme 2



In conclusion, effective one-pot syntheses of various trisaccharides have been accomplished simply by changing the solvent system during the reaction and utilizing the reactivity differences of donors in different solvents. This important solvent effect on glycosylation rates should always be considered when designing one-pot syntheses or orthogonal glycosylations based on other reactivity differences.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **6**, **7**, **8**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) **Typical experimental procedure**: NIS (1.3 equiv) was added under argon to a stirred mixture of **1** (1 equiv), **2** (1 equiv), and molecular sieves in dry Et_2O. After 30 min, a catalytic amount of AgOTf was added, and, after an additional 45 min, compound **3** (1 equiv) and NIS (1.3 equiv) dissolved in CH_2Cl_2 were added. The mixture was stirred for 15 min, whereafter a catalytic amount of AgOTf was added. After a further 15 min, the reaction was quenched by the addition of Et_3N. The resulting mixture was diluted, filtered, and concentrated, and the residue was subjected to silica gel column chromatography to yield **6** (81%).

(9) Compound **7** was obtained as an α/β 1:9 mixture according to ^1H NMR.