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Base-catalyzed Diastereoselective Trimerization of Trifluoroacetone

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Abstract

Amphiphilic fluorocarbons have unique properties that facilitate their self assembly and adhesion to both inorganic and biological substrates. Incorporation of these moieties into valuable constructs typically require complex synthetic routes that have limited their use. Here, the base-catalyzed diastereoselective synthesis of 6-methyl-2,4,6-tris(trifluoromethyl)tetrahydro-2H-pyran-2,4-diol is reported. Trimerization of trifluoroacetone in the presence of 5 mol% KHMDS delivers one of four diastereomers selectively in 81% yield with no column chromatography. Temperature screening revealed the reversibility of this trimerization and the funneling of material into the most thermodynamically stable oxane. Subsequent functionalization with boronic acids is reported.

Oxane TOC Graphic

The base-catalyzed trimerization of trifluoroacetone delivers one of four possible diastereomers of a highly fluorinated sugar analog. The reaction proceeds in high yield with no purification when run under thermodynamic control. Mechanistic considerations, crystallographic analyses, and functionalization with boronic acids are presented.

Recent advances in fluoroorganic chemistry have enabled the synthesis and evaluation of a variety of fluorinated materials, agrochemicals, and diagnostic probes that exhibit unique and complementary physical properties relative to their hydrocarbon congeners. For example, incorporating fluorocarbon moieties in polymer solar cell materials have resulted in optimized cell morphology^{1,2} and charge recombination^{3,4} while their use as surface coatings in micelles has yielded extremely robust in-vivo imaging agents.^{5–8} While the benefits of fluorination have been realized in many research areas, nowhere has it had such a

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large impact as in medicinal chemistry where substitution for hydrogen is routinely employed to modulate acidity of pendant functionality, impart lipophilicity, and block undesired oxidation.^{9–13} This is exemplified by the fact that in 2010 approximately 20% of all prescribed drugs and 30% of the top 30 blockbuster contained at least one fluorine atom.¹⁴ Of these compounds, fluorinated sugars represent only a small fraction – likely a consequence of the difficulty inherent in synthesizing them stereoselectively.^{15–19} Nevertheless, a host of biologically relevant molecules including antivirals, antineoplastics, glycosyltransferase probes,²⁰ and glycosidase inhibitors,^{21,22} containing fluorinated sugars have been developed, Figure 1.

As part of a research program aimed at developing methods for stereoselective syntheses of biologically relevant fluorinated sugars from cheap and available starting materials we investigated the base-mediated oligomerization of acetone and hydroxyacetone derivatives. The base-mediated trimerization of trifluoroacetone was first observed, and the product correctly determined, in 1954 when Henne and Hinkamp added trifluoroacetone directly to sodium metal.²³ Since then, a variety of bases^{24,25} have been shown to mediate this process – sodium amide and sodium ethoxide are notable exceptions (only dimerization occurred),²⁶ Scheme 1. In each case, a mixture of diastereomers ($\pm$)-**1a** and ($\pm$)-**2a** were formed in varying ratios depending on the base employed. Additionally, anomerization of each of these to ($\pm$)-**1b** and ($\pm$)-**2b** occurred spontaneously in solvents of sufficient polarity. A full report detailing the kinetics of this interconversion has been reported.²⁷ The inability to easily and cleanly obtain specific isomers of this fluorinated sugar have relegated this potentially useful fluorinated hexose to obscurity. Herein, we report the diastereoselective synthesis of oxane ($\pm$)-**1a**, Scheme 1, and its functionalization with boronic acids.

A screen of conditions yielded a base-catalyzed procedure that reliably generates oxane ($\pm$)-**1a** in 20:1 dr without anomerization. Table 1 shows the most striking and revealing of those conditions tried. The ratio of **1a** to **2a** was observed to decrease significantly when the reaction was run at lower temperatures. We found that running the reaction for 24 hours at RT instead of 60 °C changed the diastereomeric ratio from >20:1 in favor of ($\pm$)-**1a** to 1:1, entry 5. If the reaction was kept at 0 °C, a larger amount of ($\pm$)-**2a** was observed; 0.9:1 (**1a**/**2a**), entry 6. Taken together, these temperature experiments point to a fully reversible mechanism wherein, over 24 hours at 60 °C, the more thermodynamically stable oxane ($\pm$)-**1a** is produced almost exclusively. Indeed, we were able to quench the reaction at different points and observe this ratio decreasing over time, entries 2–4. We found this diastereomeric ratio between ($\pm$)-**1a** and ($\pm$)-**2a** to change only slightly when NaHMDS and LiHMDS were employed, although lower yields and formation of their respective anomers were observed, entries 9, 10. Tetrahydrofuran is a necessary cosolvent in this reaction – running it in 100% toluene resulted in a d.r. of 3.3:1, entry 14, with some anomerization occurring. Based on these observations we propose the reaction mechanism described in Scheme 2. Initially, deprotonation of one equivalent of trifluoroacetone generates a potassium enolate that is then involved in an aldol reaction with another equivalent proceeding through one of two Zimmerman–Traxler²⁸ transition states, **I** or **II**. It is apparent in this model that the stereodefining transition state **I**, leading to the major diastereomer ($\pm$)-**1a**, is favored over **II** due to smaller syn-pentane interactions; –CH₃ vs. –CF₃. The

minimization of syn-pentane interactions also drives the thermodynamic equilibrium toward the oxane containing an axial $-\text{CH}_3$ as opposed to an axial $-\text{CF}_3$.

That all three trifluoromethyl groups are on the same face confers ($\pm$)-**1a** with a unique amphiphilicity that results in the formation of alternating oxygen-rich and fluorine-rich planes in the solid state, Figure 2. The hydrophilic nature of the oxygen rich face coupled with the hydrophobic fluorine plane is a feature that has been recognized and exploited in a number of systems. These include the syntheses of multicompartments²⁹ and thermoresponsive³⁰ micelles, Janus dendrimers,³¹ and gels³² (among many other fluorine constructs) that enjoy a wide range of biomedical applications.^{33,34}

To allow the conjugation of this fluorinated hexose onto molecules of interest we set about installing a functional handle that we hoped would both inhibit anomerization and allow for further manipulation. As previously reported, we found ($\pm$)-**1a** to undergo anomeric equilibration in the presence of organic bases and sufficiently polar solvents.²⁷ This severely limited our ability to perform chemistry on the diol handle and restricted us to investigating base-free conjugation methods, some of which are outlined in the Supporting Information (Figure S1). This stands in contrast to the base-mediated functionalization of a related series of perfluorinated oxanes containing a 1,5-diol (instead of the 1,3-diol presented by the oxanes herein) that cannot unravel, Scheme 3.^{35,36} Interestingly, the 1,5 diol ($\text{pK}_a = 5.4$)³⁵ is 10000-fold more acidic than ($\pm$)-**1a** ($\text{pK}_a = 9.4$).²⁷ The abnormally low pK_a of perfluorodiol is attributed to strong intramolecular hydrogen bond stabilization of the resulting alkoxide.³⁷ Given that both oxanes participate in similar intramolecular hydrogen bonding, (see Figure 2 and Figure S2) the drastic difference in acidity between these two oxanes is very peculiar. It has been shown for fluorine alcohols that steric bulk decreases H-bonding capacity while leaving Brønsted acidity relatively unaffected.³⁸ The present situation represents a novel combination of these effects given that H-bonding within fluorine diols directly impacts Brønsted acidity. Thus, we attribute the low acidity of ($\pm$)-**1a** to the axial methyl group (absent in the 1,5-diol) that affects the local hydrophobic environment and solvation of the 1,3-diol.

In terms of synthetic manipulation of ($\pm$)-**1a**, tris(pentafluorophenyl)borane-catalyzed silylations³⁹ and acid-catalyzed acylations and condensations with acid chlorides, aldehydes, and acetals all failed with the exception of direct acetylation (see SI; ($\pm$)-**3**) in neat acetyl chloride. The only method we found to reliably functionalize this fickle diol was condensative borylation.⁴⁰ Heating oxane ($\pm$)-**1a** at 110 °C in the presence of boronic acids in toluene for 24 hours delivered the borylated species in generally good yields, Scheme 4. These borylated oxanes are hydrolytically unstable to silica, alumina, and water and thus could not be purified via extractive workup or chromatography. Luckily, very few by-products are generated during the reaction and purification is usually unnecessary. In the case of solid borates, very pure material can be obtained by trituration with hexanes, albeit with some product loss, ($\pm$)-**4a–4f**. Overall, electron rich and poor aryl boronic acids, as well as vinyl boronic acids worked well in this condensation while sterically encumbered aryl boronic acids and aliphatic boronic acids failed to react and decomposed, respectively.

Conclusion

In summary, we have developed conditions for the KHMDS-catalyzed trimerization of trifluoroacetone to generate hexose-like fluorinated oxane ($\pm$)-**1a** in >20:1 dr on a 100 mmol scale. Optimization of the reaction conditions revealed the complete reversibility of this trimerization and the funneling of material toward the most thermodynamically stable diastereomer. Work directed at functionalizing this oxane resulted in the reliable borylation of the cis-diol motif using simple boronic acids. The ease of synthesis and amphiphilic nature of ($\pm$)-**1a** motivate us to further control anomerization and facilitate its conjugation onto relevant organic scaffolds. Studies directed toward taking advantage of this unique fluorinated amphiphile in non-covalent macromolecular recognition is currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Biologically relevant fluorinated sugars.

Figure 2.
X-ray crystal structure of (±)-**1a** showcasing its alternating hydrophilic and hydrophobic faces.

This work

Previous work

Scheme 1.
Current and previous work.

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Scheme 3.

Previously reported synthesis and functionalizations of related perfluorinated oxanes containing a 1,5-diol motif.³⁶

Scheme 4.
Substrate scope of borylation.

Table 1

Screening results.

Entry	Deviation from Standard ^a	(±)-1a	(±)-1b	(±)-2a	(±)-2b	Yield ^b
1 ^c	none	>20	0	1	0	81%
2 ^c	60 °C for 16 h	>20	0	1	0	76%
3 ^c	60 °C for 8 h	12.5	0	1	0	70%
4 ^c	60 °C for 1 h	2.6	0	1	0	65%
5	RT for 24 h	1	0	1	0	72%
6	0 °C for 24 h	0.9	0	1	0	69%
7	-78 °C for 24 h	- Complex Mixture -				33% ^d
8 ^c	1 M	>20	0	1	0	66%
9	5 mol % NaHMDS	>20	<0.2	1	<0.2	62%
10	5 mol % LiHMDS	>20	0.5	1	0.5	55%
11	2:1 (THF/PhMe)	>20	0	1	0	68%
12	1:1 (THF/PhMe)	>20	0	1	<0.2	63%
13	1:2 (THF/PhMe)	>20	0	1	0	65%
14	PhMe	3.3	<0.1	1	<0.2	60%

^aStandard conditions: trifluoroacetone (1.00 mmol, 1.00 equiv.), KHMDS (0.05 mmol, 0.05 equiv.), THF (3.00 mL final volume; 0.33 M), 60 °C for 24 hours. KHMDS: potassium bis(trimethylsilyl)amide; THF: tetrahydrofuran.

^bIsolated yield.

^c10 mmol scale at 1M concentration.

^dUndetermined products. Ratio of isomers determined using ¹H NMR and ¹⁹F NMR.