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The reaction of O-silylated cyanohydrin anions with epoxides as an alternative for the enantio- and diastereoselective preparation of aldols

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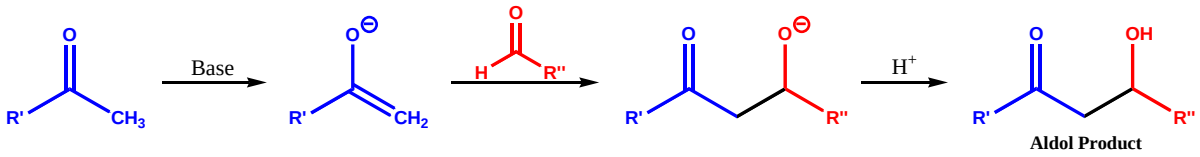
ABSTRACT

The aldol addition is one of the most important and most utilized carbon-carbon bond forming reactions in chemical synthesis. This reaction, between an aldehyde or ketone and a second, enolized aldehyde or ketone, results in the formation of a β-hydroxycarbonyl (often referred to as an "aldol product" or "aldol"). Modern variations of the aldol reaction have allowed for enantio- and diastereoselectivity in the reaction; however, many of these methods have undesirable drawbacks such as the use of expensive chiral auxiliaries. The chiral auxiliaries require additional synthesis steps for their introduction and removal and cannot be completely recovered after the reaction is complete. Methods for the preparation of aldol products that do not involve enolate chemistry have also been developed. Here we propose the reaction of O-silylated cyanohydrin anions with epoxides as an alternative to the aldol addition for the preparation of β-hydroxycarbonyls. By taking advantage of excellent, established asymmetric epoxidations, this method allows for high degrees of enantio- and diastereoselectivity in a highly atom economical way. We report here the optimization of the reaction conditions and the initial scope and limitations of the epoxide electrophiles.

INTRODUCTION

The aldol addition is a common and important carbon-carbon bond forming reaction used in chemical synthesis. The reaction occurs between an aldehyde or ketone and a second, enolized aldehyde or ketone resulting in the formation of a β-hydroxycarbonyl, commonly referred to as an "aldol product." The reaction can result in the formation of up to two new chiral centers, giving rise to as many as four stereoisomeric products (syn / anti).

Scheme 1. Aldol Addition

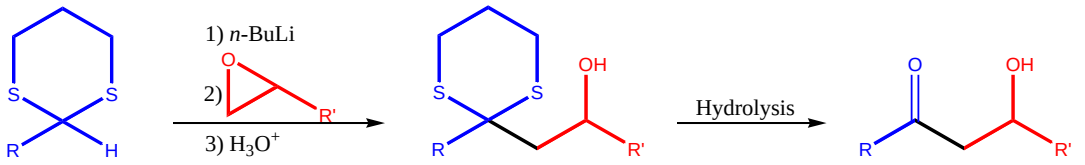


Modern variations of the aldol reaction have been developed, such as those by Evans[1] and Crimmins[2], which allow for significant diastereoselectivity in the reaction but require expensive chiral auxiliaries and necessitate additional steps for their introduction and removal. Catalytic, asymmetric aldol reactions have also been developed, particularly "Mukaiyama" aldol reactions[3] using chiral catalysts. Organocatalytic aldol reactions such as the Hajos-Parrish method[4], also offer an enantio- and diastereoselective route to aldol formation.

Methods for the preparation of aldol products that do not involve enolate chemistry have also been developed. The "non-aldol aldol" reaction of Jung[5] utilizes the rearrangement of epoxides to give aldols and has advantages in enantio- and diastereoselctivity; however, its synthetic utility is limited in that it does not involve the formation of a carbon-carbon bond. A useful approach to aldols that does involve formation of a carbon-carbon bond is the reaction of acyl anion synthons with epoxides. Well-known acyl anion synthons are the dithiane anions[6] that are easily prepared from aldehydes and can be

deprotonated with powerful bases such as *n*-butyllithium. The reaction of the resulting anion with an epoxide and subsequent hydrolysis of the adduct furnishes an aldol.

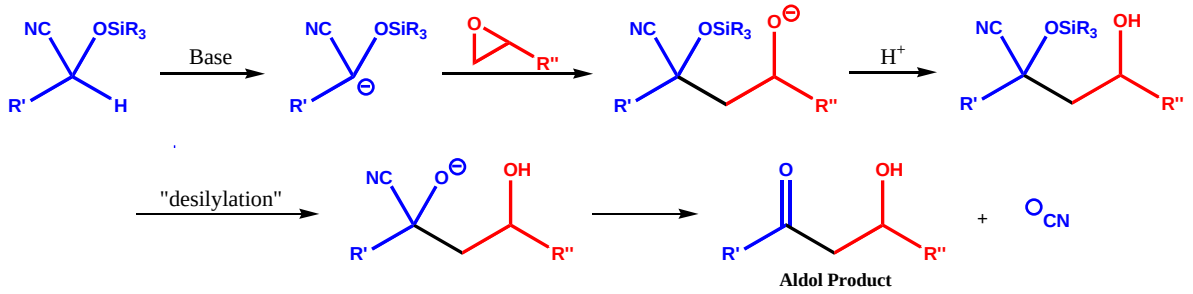
Scheme 2. Reaction of Dithiane Anions with Epoxides



Utilizing epoxides as the electrophile is a significant advantage of this 'acyl anion' strategy. The epoxides can be prepared enantio- and diastereoselectively using one of the many well-established asymmetric epoxidations such as those by Jacobsen, Sharpless and Shi.[7] During the reaction with the acyl anion synthon, the stereochemical configuration at the β-carbon is completely retained while that at the α-carbon is predictably inverted. This provides an excellent route to the enantio- and diastereoselective formation of aldol products.

While a very useful method, problems do exist with the specific use of dithianes as the acyl anion synthon. Problems include the challenging hydrolysis of the dithiane, complications pertaining to the nucleophilicity of sulur that can introduce undesired side reactions and the unfavorable odor of the 1,3-propanedithiol used to prepare the dithianes. The goal of this project is the achievement of an efficient two-step alternative method for the enantio- and diastereoselective preparation of aldols *via* the reaction of protected cyanohydrins with epoxides.

Scheme 3. Aldol Reaction of O-Silylated Cyanohydrin Anions with Epoxides



LITERATURE REVIEW

Protected cyanohydrins have been used as synthetic acyl anion equivalents and have successfully been reacted with various electrophiles including alkyl halides and carbonyls. There are however only three isolated examples of protected cyanohydrins reacting with epoxides that have been reported.

The first, by Hünig who demonstrated in 1979 that TMS-protected mandelonitrile could be successfully deprotonated and reacted with various electrophiles. Hünig attempted the reaction with three epoxides (2-butene oxide, 2-methylpropene oxide, and styrene oxide), but failed to provide the expected adduct. The second, by Rychnovsky[9] in 1997, who used acetonide-protected hydroxycyanohydrins in alkylation reactions. While alkyl halides were found to be excellent electrophiles in the reaction, alkylation with an epoxide (1,2-epoxyhexane) gave only 8% desired adduct. The third reported example was in 2007 by Takahashi[10] who successfully alkylated the epoxyethyl acetal protected cyanohydrin of acrolein with the highly reactive epoxide epichlorohydrin.

A thorough review of the literature was performed to ensure similar research has not been done elsewhere and to help ensure the feasibility of this proposed mechanism.

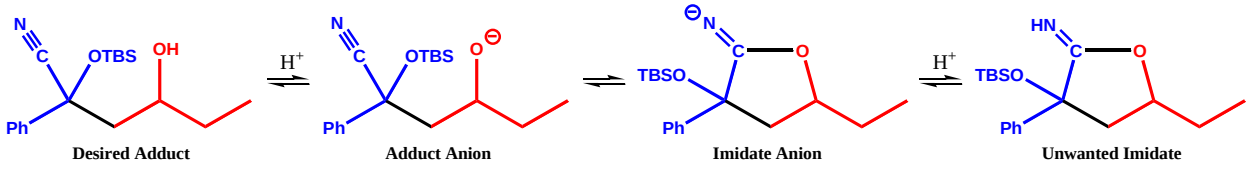
Prior Research

Our initial experiments mimicked those of Hünig[8b] in order to gain insights into the reactions and determine the actual products formed. Initial experiments were performed using TMS-protected mandelonitrile. This substrate was treated with LiHMDS in THF to effect deprotonation, and the resulting anion was reacted with 1,2-epoxybutane. The reaction failed to provide any of the desired adduct and instead produced 3-hydroxypentanenitrile as the major product, likely from the decomposition of the substrate and the subsequent nucleophilic attack of cyanide on the epoxide. Repeating the reaction in toluene as the solvent suppressed formation of the undesired 3-hydroxypentanenitirle and formed the desired adduct as a minor product along with significant amounts of benzoin and benzoin TMS ether.

The more robust TBDMS-protected mandelonitrile was prepared and then treated with LiHMDS in toluene to effect deprotonation, and the resulting anion reacted with 1,2-epoxybutane. This reaction provided none of the undesired 3-hydroxypentanentirle or benzoin byproducts, instead giving two major product types identified as the desired adduct and a cyclic imidate in a 1:1 mixture of diasteromeric pairs.

The imidate formation was the result of the intramolecular attack of alkoxide onto the nitrile moiety of the initially formed adduct. After a series of experiments, it was determined that a slow subsurface quench of the reaction with saturated aqueous ammonium chloride suppressed the formation of the cyclic imidate.

Scheme 4. Desired Adduct and Imidate Intramolecular Attack

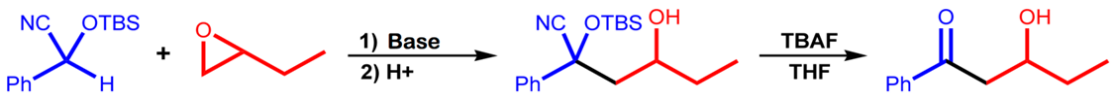


A series of experiments was performed in an attempt to suppress the formation of imidate. It was determined that a slow subsurface quench of the reaction with saturated aqueous ammonium chloride disfavored equilibration to the cyclic imidate, providing the desired adduct and imidate in an excellent 27:1 ratio. The crude product could then be desilylated using TBAF to give the desired aldol in 77% yield (two steps) after column chromatography.

RESULTS

Optimization of Conditions

The optimal conditions for the formation of aldol products from O-silylated cyanohydrins and epoxides were determined by reacting mandelonitrile TBS ether with 1,2-epoxybutane in various solvents, bases and at different temperatures. The conditions for the reaction were optimized to maximize the yield of aldol adduct and minimize the formation of the undesired imidate anion.

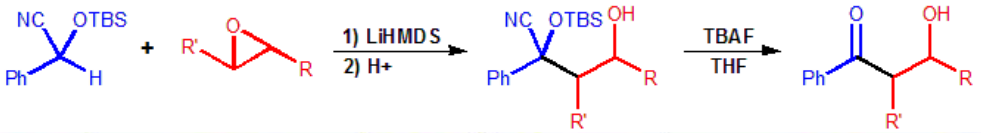


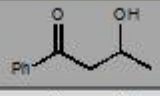
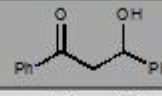
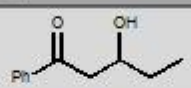
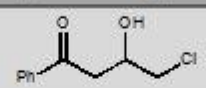
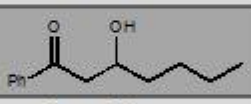
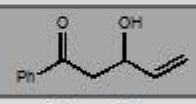
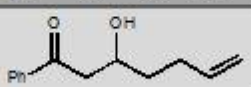
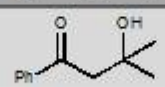
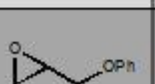
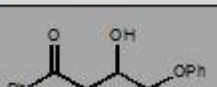
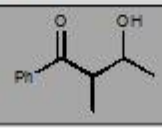
Entry	Solvent	Base	Adduct:Imidate[a]
1	Toluene	LiHMDS	9:1
2	THF	LIHMDS	4:1
3	THF	LiHMDS[b]	N/A
4	THF	LDA[b]	N/A
5	Ether	LiHMDS	6:1
6	Toluene	KHMDS	N/A
7	Toluene	LiHMDS[c]	3:1
8	Toluene	LiHMDS[d]	5:1

[a] Determined by ^{1}H-NMR
[b] The reaction was treated with TBAF before quenching
[c] The reaction was treated with TMEDA before quenching
[d] The reaction was treated with cobalt (II) chloride before quenching

Scopes and Limitations

Various epoxides were reacted with mandelonitrile TBS ether under the optimized conditions.



Epoxide	Product	Yield (%)	Epoxide	Product	Yield (%)
		53			0
		84			0
		90			0
		70			52[a]
		60			56[a]

[a] Reaction run at -40 °C

DISCUSSION

The best results were found using toluene or ether as the solvent and LiHMDS as the base. Reactions run at room temperature usually gave good yields with a few exceptions. The ratio of desired adduct to cyclic imidate was enhanced at -40 °C when reacting 2,2-dimethyloxirane. The optimal conditions for the reaction of O-silylated cyanohydrins with epoxides were determined to be using ether solvent and LiHMDS base followed by subsurface quenching with ammonium chloride and then desilylation with TBAF.

Various epoxides were reacted with mandelonitrile TBS ether under the optimized conditions. Yields were generally very good and the aldols were of excellent purity. For future work, the generality of the method will be further demonstrated by reacting more epoxides with the mandelonitrile TBS ether under the optimized reaction conditions. The use of other protected cyanohydrins will also be investigated. The optimal conditions will be applied to a variety of other appropriate substrates, each prepared from an aldehyde using known chemistry.

The ease of preparation of O-silylated cyanohydrins from simple aldehydes, and of epoxides from alkenes makes this a very attractive alternative approach. The variety of well established, highly stereoselective epoxidation procedures empowers this stereospecific reaction to be a simple and powerful enantio- and diastereoselective approach to aldol products. The proposed mechanism provides procedurally simple methods for the selective preparation of aldols from readily available aldehydes and epoxides.

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a JEOL ECA-400 spectrometer using chloroform-D and are reported in parts per million. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quarter, m = multiplet, b = broad), coupling constant (Hz), and integration. Flash chromatography was performed using 4-6 inch packed 230-400 mesh Grade 60 silica gel column. Thin layer chromatography was performed using TLC Silica gel 60 F_{254} plates. Solvents were dried prior to use and when necessary glassware was flame dried. The epoxides used were dried over 4Å molecular sieves prior to use. All reactions were performed under argon.

General Preparation of the Mandelonitrile TBS Ether.

Mandelonitrile (2.66 g, 20.0 mmol) was dissolved in THF (10 mL). A 1.0 M solution of TBSCl in THF (24 mL, 24 mmol) was then added, followed by 1.634 g of imidazole in portions. The reaction was allowed to stir under argon overnight. The THF was then evaporated using rotary evaporation. Hexanes (50 mL) were then added and the solid residue removed via vacuum filtration. The filtrate was collected and the hexanes removed using rotary evaporation. The oily residue was purified via flash chromatography (20% EtOAc/Hexanes) to give a yellow oil (4.075g, 82% yield). ^{1}H-NMR: 0.14 (s, 3H), 0.22 (s, 3H), 0.98 (s, 9H), 5.51 (s, 1H), 7.36-7.47 (m, 5H).

General Alkylation of the Mandelonitrile TBS ether: Formation of Initial Adduct

Mandelonitrile TBS ether (1.0 mmol, 0.247g) was dissolved in 5mL of solvent and treated with base (1.2 equiv) by drop-wise addition at the indicated temperature. The epoxide (2.0 equiv) was added drop-wise and the contents of the reaction flask immediately transferred (subsurface) into 10 mL of vigorously stirred saturated aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane. The organic layers were combined and dried over anhydrous sodium sulfate. The solvents were removed using rotary evaporation. Characterization of the desired adduct was performed using ^{1}H-NMR.

General Desilyation of Initial Adduct: Formation of Desired Aldol.

The adduct prepared from the alkylation reaction was dissolved in 5 mL of THF while stirring. TBAF (1.2 mL) was added dropwise while stirring under argon. After 20 minutes, distilled water (5 mL) was added to the flask followed by 5 mL of ethyl acetate. The aqueous layer was extracted with dichloromethane. The organic layers were then combined and dried over anhydrous sodium sulfate. The solvents were removed using rotary evaporation. Column chromatography was used to purify the crude aldol product. Characterization of the desired aldol product was performed using ^{1}H-NMR, C^{13}-NMR, and IR.

ACKNOWLEDGMENTS

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