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Triethysilyl Enol Ethers in the Synthesis of Carbapenem Precursors

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Abstract

A diastereoselective process for the formation of intermediates suitable for the preparation of C1 substituted carbapenems was developed. The process is readily scalable and does not involve organometallics or strong bases such as LDA.

Keywords

Antibiotic; Carbapenem; β -Lactam; silyl enol ether; Lewis acid

The carbapenem class of β -lactam antibiotics represent the most potent and generally broad spectrum of all β -lactams¹ and these drugs are usually reserved for use in a nosocomial setting as agents of last resort. Unfortunately, in the past two decades, potent carbapenemases, both serine and metallo, have emerged in highly resistant Gram-negative pathogens, including carbapenem resistant Enterobacteriaceae (CRE),² *Pseudomonas aeruginosa*,³ and *Acinetobacter baumannii*.⁴ The SAR of the carbapenem class was optimized during the 1970s and 1980s before these highly resistant pathogens had emerged.

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Thus we decided to take a closer look at whether atypical (i.e. substituted at positions other than C2) carbapenem analogs might have improved biological profiles.

Carbapenems are totally synthetic antibiotics, the synthesis of which is facilitated by the commercial availability of (3*S*,4*R*)-4-acetoxy-3-[(*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]azetidine-2-one (**1**) which can react with a wide array of nucleophiles, including some silyl enol ethers, such as **2**,⁵ to generate the key C1-C5 C-C bond with the appropriate C5 configuration, presumably via an intermediate acyliminium ion as shown in Scheme 1.

We desired to find a general, easily scalable, methodology for forming this crucial C-C bond that did not involve organolithium reagents. Ideally, the methodology would facilitate manipulation of the C1 substituent, would provide opportunity for stereochemical control at this position, and would omit potentially sensitive functionality, such as the diazo moiety of **2**, which might interfere with subsequent synthetic manipulations prior to closure of the pyrrolidine ring. A two carbon fragment which terminated in a functional group suitable for further elaboration of the pyrrolidine ring would be ideal. Thus our target was a simple intermediate such as **4** (Scheme 2). Inspection of the literature revealed that this problem has been solved by utilization of silyl ketene acetals (**5**),⁶ silyl enol ethers of chiral carboximides (**6**),⁷ and organozinc reagents (**7**).⁸ The acetate **1** can also be allylated under indium-mediated conditions.⁹

We proceeded to explore these options. Formation of silyl ketene acetals, such as **5**, and silyl enol ethers of carboximides, **6**, employ LDA as the base. This was deemed unsuitable for large scale synthesis, as generation of LDA itself involves use of *n*-butyllithium, and, in our experience commercial LDA solutions are unstable to long term storage. Our attempts to convert esters to silyl ketene acetals utilizing weaker bases, such as triethylamine, together with more potent silylating agents, such as silyl triflates were unsuccessful.¹⁰ Utilization of organozinc reagents, **7**, initially seemed promising, and small scale (i.e. < 5 mmol) syntheses were successful. However, these reagents posed substantial hazards on scale-up. Reaction of activated zinc with bromoesters efficiently occurs only at slightly elevated temperatures (> 50 °C), and is, itself, exothermic. Thus large scale reactions (> 200 mmol) involving this methodology proved difficult to control and these reagents were deemed unsuitable.

By contrast, silyl enol ethers of aldehydes and ketones are readily available through reaction of the carbonyl compound with an appropriate silylating reagent in the presence of triethylamine, and, as exemplified by the precedent in Scheme 1, should react with **1** under mild conditions. Initially, we envisioned that silyl enol ethers of pyruvic acid esters might make suitable precursors, after subsequent deprotection and oxidation to the desired substituted acetates (Scheme 3). However, while the TBS enol ether of benzyl pyruvate (**9**) readily formed, it refused to react with **1**, even at elevated temperature (higher temperatures led to substantial decomposition of **1**). Presumably, the electron withdrawing effect of the adjacent ester functionality renders the double bond less electron rich, thereby interfering with this process.

We then envisioned a more direct process involving silyl enol ethers of acetaldehyde, which could react with **1** to form the aldehyde **13**, and then be subsequently oxidized to the acid or reduced to the corresponding alcohol. Surprisingly, the reaction of **1** with aldehyde silyl enol ethers has not been reported. Vinyloxytrimethylsilane (**12a**) is commercially available, but extremely expensive (5 g/\$101 USD, Sigma-Aldrich, bp 74 °C), with the high cost due to its challenging synthesis¹¹ including difficult separation from solvents due to its low boiling point. Gratifyingly, as shown in Equation 1, the reaction of **1** with **12a** proceeded smoothly, yielding a mixture of **13**, **14a**, and unreacted **1**. To circumvent the difficult preparation and high cost of **12a**, we decided to prepare and employ the TBS enol ether **12b**. Unfortunately, the TBS enol ether was substantially less reactive than **12a**, and produced only a poor yield of **13**, together with **14b**. An optimal compromise of ease of preparation and isolation was produced by utilizing the triethylsilyl (TES) ether, **12c**. Synthesis of **12c** was achieved by treating freshly distilled acetaldehyde with triethylsilyl chloride and triethylamine in dry acetonitrile and purification (removal of TESOH) was accomplished using flash chromatography using pentane as eluent.¹² Unlike trimethylsilyl ethers, triethylsilyl ethers are stable to column chromatography.¹³

Likewise we were able to utilize this methodology to generate a number of substituted silyl enol ethers as shown in Table 1. Starting aldehydes, **17** and **18**, were generated from the monoprotected diols, followed by Swern oxidation,¹⁴ as shown in Equation 2. Lastly, we were able to form the triethylsilyl bromoenol ether **23**, by utilizing a two-step bromination-elimination sequence¹⁵ as shown in Equation 3.

As shown in Table 2, zinc-promoted reaction of the individual stereoisomers with **1** provided the corresponding aldehydes, with, in the case of **19**, a surprisingly high degree of diastereocontrol. Since diastereomeric aldehydes **24a** and **24b** are inseparable by column chromatography, and to confirm stereochemical identity the aldehyde was selectively reduced using NaBH₃CN as shown below and the resultant, chromatographically separable, alcohols, **27a** and **27b**, and the major isomer, **27a**, proven identical by ¹H NMR with the reported spectra for this epimer.¹⁶ These alcohols were individually further converted to bicyclic β-lactams **28a** and **28b** as indicated in Scheme 4, with the major isomer again proving identical with previously reported spectra.¹⁷ A functionalized aldehyde (i.e. R = OR'), potentially useful in C1-substituted carbapenem synthesis, was formed by using (Z)-1,2-bis(triethylsilyloxy)ethylene, **21**, as the silyl enol ether, but reaction occurred only at elevated temperature (85 °C) in the absence of solvent (with the diethyl ether solvent of the ZnCl₂ allowed to distill from the reaction vessel).

Unfortunately, (Z)-1,3-bis(triethylsilyloxy)-1-propene, **22**, produced the unexpected substitution product, **26**, presumably due to ZnCl₂ promoted decomposition of the [γ]-substituted silyl enol ether, and (Z)-1-bromo-2-triethylsilyloxyethylene, **23**, refused to react, even under forcing conditions.

Lastly, since we were unable to couple triethylsilyl bromoenol ether **22**, we decided to try to brominate aldehyde **13**, to generate a C1-substituted carbapenem synthon. As shown in Scheme 5, this was successfully achieved by converting **13** to the trisilylated enol ether **29**,

and then treating with NBS to produce an inseparable 4:1 mixture of diastereomers **30a** and **30b**.¹⁸

Discussion

Silyl enol ethers of aldehydes are less frequently utilized in Mukaiyama aldol reactions since the resultant product aldehyde can itself undergo reaction with the enol ether resulting in lowered yields¹⁹ and forming oligomers.²⁰ The Mukaiyama-like reaction of aldehyde triethylsilyl enol ethers and **1** presented herein has advantages in that the iminium ion intermediate (Scheme 1) may be more reactive than the product aldehyde, thus allowing for selectivity and improved yields. Secondly, the use of triethylsilyl enol ethers has advantages, since TES enol ethers are readily prepared, chromatographically stable, and have enhanced reactivity relative to TBS enol ethers.

In conclusion, we have developed a new method for forming the carbapenem C1-C5 bond using silyl enol ethers which, in the case of C2 substituted silyl enol ethers, is capable of producing the product with high diastereoselectivity. We have discovered that vinyloxytriethylsilane (**8c**) is an easily prepared and cost effective substitute for vinyloxytrimethylsilane, **8a**, an acetaldehyde equivalent that has been extensively employed in organic synthesis, despite its challenging preparation and high cost. Lastly we have generated a number of highly functional carbapenem precursors that we anticipate will be useful in the preparation of C1 modified carbapenem antibiotics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Current commercial carbapenem antibiotics with conventional numbering scheme

Scheme 1.
Reported synthetic methodology leading to **3**.

Scheme 2.
Reported synthetic methodology leading to **4**.

Scheme 3.
Attempted synthesis of intermediates **10** and **11**.

Equation 1.

Initial results of reaction of selected vinyloxytrialkylsilanes with **1**.

Equation 2.

Swern oxidation of monotriethylsilylated diols **15** and **16**.

Equation 3.
Bromination of **12c**.

Scheme 4.

Conversion of **24** to reported compounds for stereochemical verification

Scheme 5.
Bromination of **12**

Table 1

$\text{R}-\text{CH}_2-\text{CHO} \xrightarrow[\text{CH}_3\text{CN, rt to 65 } ^\circ\text{C}]{1.2 \text{ eq TESCl, 1.5 eq Et}_3\text{N}} \text{R}-\text{CH}=\text{CH}-\text{OTES}$			
R	TES enol ether	Temperature	Yield
H	12c	rt to 35 °C	62%
CH ₃	19 + 20	65 °C	54%
OTES (17)	21	65 °C	35%
CH ₂ OTES (18)	22	65 °C	49%

Table 2

Reaction of TES enol ethers with 1.

Enol Ether	Product(s)	Temperature	Yield
12c	13	40 °C	32%
19	6 1	40 °C	48%
20	3 2	40 °C	56%
21	25a 25b
22	26	85 °C 85 °C	84% 64%
23	No reaction	85 °C	-	