ORGANIC LETTERS

2001
Vol. 3, No. 16
2529−2531

Novel [1,2]- and [2,3]-Wittig Rearrangements of α-Benzyloxy β-CF_3-β-lactam Enolates

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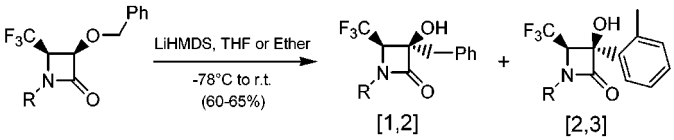
Received May 30, 2001

ABSTRACT



α-Benzyloxy α-CF_3-β-lactams are shown to offer the first examples of the enolate [1,2]- and enolate *ortho*-[2,3]-Wittig rearrangements which provide a unique entry to the α-benzyl-α-hydroxy lactams and the α-aryl-α-hydroxy lactams, respectively. Both products are potential precursors of new trifluoromethyl isoserines, and the latter is not accessible via the usual alkylation methodology.

Alkylation of β-lactams is a powerful and efficient method for the diastereoselective preparations of α-branched β-lactams and nonproteogenic α-alkyl amino acids.[1,2] However, this alkylation reaction is mostly described for the cases of α-amino- and α-hydroxy-substituted β-lactams.[3] The α-branched substitution could serve as conformational modifier, bringing about structural constraints[4] and/or more resistance to both chemical and enzymatic hydrolysis than the parent β-lactams.[5] In this connection, α-branched isoserines such as norstatine analogues could be interesting amino acid residues for protease inhibitors[6] and taxol derivatives.[2,7]

We have recently reported the preparation of both racemic and nonracemic β-fluoroalkyl α-benzyloxy β-lactams through the ketene−imine cycloaddition of fluoroalkyl imines.[8,9] These β-lactams have been used for the preparation of new active docetaxel derivatives[10] and of HIV-1 protease inhibitors,[11] and hence we became interested in the substituent effect of these compounds on biological activities.

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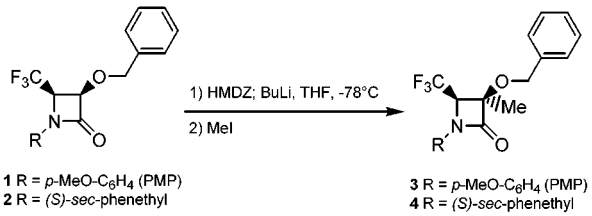
10.1021/ol016198p CCC: $20.00
Published on Web 07/17/2001

We communicate here the results observed during investigations on the alkylation of racemic and nonracemic β-trifluoromethyl β-lactams **1** and **2**, namely the unprecedented [1,2]- and [2,3]-Wittig rearrangements of their enolates.

Enolates of β-lactams **1** and **2** were generated with LiHMDS (2.5 equiv) in THF at −78 °C (Scheme 1), and

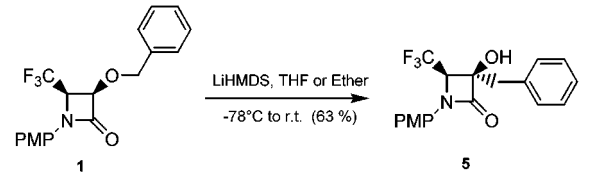
Scheme 1



their quenching with methyl iodide provided the α-methyl-β-lactams **3** and **4** in excellent yields (93% and 90%, respectively). The reaction is stereoselective, and alkylation occurs exclusively from the side opposite the bulky trifluoromethyl substituent.[12] Only traces of the other stereoisomer were detected.

However, when less reactive electrophiles such as propyl halides (bromide and iodide) were used, the alkylation failed at temperatures ranging from −78 to 20 °C, and the starting materials were recovered together with significant amounts of new products resulting from the enolate rearrangements (vide infra). Since the Wittig rearrangements of enolates of α-benzyloxy carbonyl systems had never been observed,[13,14] we explored the rearrangement behavior of the enolates of **1** and **2**. The enolate of **1** was generated with LiHMDS (2.5 equiv) in THF at −78 °C. At that temperature, no reaction occurred, even after 2 h. When the mixture was gradually warmed, the disappearance of the enolate started at −30 °C (checked after hydrolysis). After 1 h at room temperature, the reaction was complete, yielding the rearrangement product **5** as a single diastereoisomer with no trace of any other product. **5** was isolated in 63% yield (Scheme 2). The

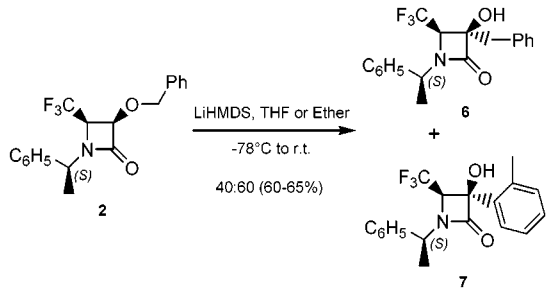
Scheme 2



configuration was deduced from NOESY experiments by the presence of a correlation between β-H and the benzylic protons, indicating their proximity.

Interestingly enough, the enolate of the *N*-[(*S*)-*sec*-phenethyl]-(*R*,*R*)-β-lactam **2** was found to rearrange into two compounds, **6** and **7**, in a 40:60 ratio, both as a single diastereoisomer (Scheme 3). Isomers **6** and **7** were isolated

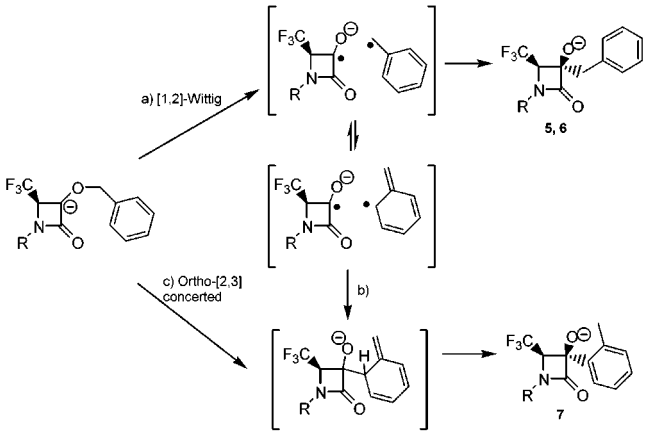
Scheme 3



as a mixture (65%). The stereochemistry of **7** was determined from NOESY experiments: β-H correlates with the *ortho*-proton and the tolyl-methyl protons.

Products **5** and **6** obviously arise from the classic [1,2]-Wittig rearrangement which is known to proceed via a radical cleavage−recombination pathway (Scheme 4).[13,14] To the

Scheme 4



best of our knowledge, it is the first example of the [1,2]-Wittig rearrangement involving an enolate as the migrating terminus, while the [2,3]-Wittig sigmatropic versions involving enolate termini have ample precedents.[13,15] Significantly, the rearrangement occurs with complete retention of configuration at the migrating terminus (pre-enolate carbon), while partial inversion of configuration has generally been observed in the [1,2]-Wittig rearrangements on sp^3-carbanion termini, despite the radical process.[16] It thus appears likely

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that the steric course of the present [1,2]-Wittig process is governed by steric hindrance offered by the β-CF_3-substituent on the β-lactam ring as observed for the aforementioned alkylation reactions.

Also interesting and rather surprising is the formation of product **7** which is best explained as a result of the "*ortho*-[2,3]-Wittig" sigmatropy involving the double bond of the phenyl group as part of the migrating group, although the radical dissociation−recombination pathway cannot completely be excluded (Scheme 4). Various types of α-allyloxy carbanions, including enolate ones, are well-known to readily undergo the [2,3]-Wittig sigmatropic rearrangement which currently enjoys wide application in organic synthesis.[13,15] However, the "*ortho*-[2,3]-Wittig" rearrangement of α-benzyloxy carbanions should be kinetically less favorable due to the involvement of the dearomatization step and also due to the great migratory aptitude of the benzyl group in the [1,2]-Wittig shifts.[16d] Indeed, only a few examples of such *ortho*-[2,3]-Wittig rearrangements have been reported thus far.[17,18] In contrast, *ortho*-[2,3]-shifts have ample precedent such as the thia-[2,3]-Wittig rearrangement of α-benzylthioalkyllithiums[19] and the Sommelet−Hauser rearrangement of *N*- and *S*-benzyl ylides.[20]

In this regard, the present observation of the enolate *ortho*-[2,3]-Wittig rearrangement is remarkable and it proceeds with complete stereocontrol to afford **7** as a single stereoisomer via exclusive C−C bond formation from the side opposite the sterically demanding CF_3.

In view of the recent observations on the influence of reaction conditions on competing processes,[17c,18b] we attempted to enhance the *ortho*-[2,3]-shift preference. For **1** and **2**, use of Et_2O instead of THF resulted in no effect at all on the course of the enolate rearrangements. More strikingly, no effect of reaction temperature was observed: the **6**:**7** ratios were essentially the same at −30 °C and higher temperature, although it is well established that a lower temperature favors the concerted processes. Thus, these observations led us to suggest that the present *ortho*-[2,3]-Wittig shift is likely to proceed via the radical pathway (cf. Scheme 4). If so, nature of the *N*-substituent may act upon stability and reactivity of the β-lactam radical which can be considered as a captodative species. This could explain why the *ortho*-[2,3]-shift prevails over the [1,2]-shift in the case of β-lactam **2** (*N*-phenethyl), while β-lactam **1** gave only the [1,2]-Wittig product.

In summary, we have presented the first examples of the enolate *ortho*-[2,3]-Wittig and/or enolate [1,2]-Wittig rearrangement by using β-lactams as substrates. From a synthetic point of view, the present Wittig rearrangements provide a unique entry to α-benzyl-α-hydroxy-β-CF_3-β-lactams and the α-aryl-α-hydroxy-β-CF_3-β-lactams, respectively, which are potential precursors of new trifluoromethyl isoserines, and the latter product is not readily accessible via the usual alkylation methodology.

Supporting Information Available: Experimental procedures and full characterization (IR, ^1H, ^{13}C, ^{19}F NMR spectra and analysis) for compounds **3**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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