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A NOVEL CARBON–CARBON BOND FORMATION AT THE C4 POSITION OF β-LACTAMS. FLUORIDE ION INDUCED DESILYLATIVE α-HYDROXYALKYLATION OF 3-ALKYLIDENE-4-TRIMETHYLSILYLAZETIDIN-2-ONES WITH ALDEHYDES

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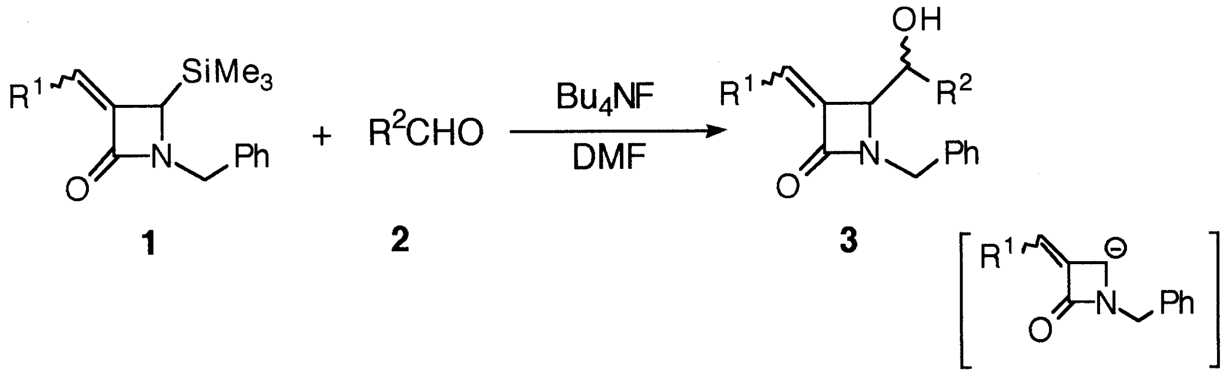
The reaction of 3-alkylidene-4-trimethylsilylazetidin-2-ones with aldehydes in the presence of fluoride ion gave 3-alkylidene-4-(α-hydroxy)-alkylazetidin-2-ones in good to moderate yields.

KEY WORDS β-lactam; desilylative α-hydroxyalkylation; 3-alkylidene-4-trimethylsilylazetidin-2-one; 3-alkylidene-4-(α-hydroxy)-alkylazetidin-2-one; aldehyde; fluoride ion

Much attention has recently been directed toward the exploration of synthetic strategies for non-classical β-lactam antibiotics such as thienamycin, PS-5 and the related carbapenems because of their powerful physiological activities and pharmacological properties.[1)] One of the fundamental subjects in the synthetic studies on these compounds is how to introduce a carbon substituent into the C4 position of azetidin-2-ones, and considerable attention has been paid to this subject.[2–4)] Although substitution reactions with carbon nucleophiles, *e.g.*, enol silylethers, allyltin reagents, carbene species, *etc.*, are well-established processes for the carbon–carbon bond formation at the C4 position of azetidin-2-ones,[2)] electrophilic carbon–carbon bond formation at the C4 position is very much limited.[3, 4)] We report here electrophilic substitution of 3-alkylidene-4-trimethylsilyl-azetidin-2-ones (**1**)[5)] with aldehydes (**2**) in the presence of Bu_4NF to give 4-(α-hydroxy)alkyl derivatives (**3**) in good yields (Chart 1). In this reaction, the carbon–silicon bond is selectively cleaved by fluoride ion to give the corresponding carbanion **A** which can react with **2**, providing **3**.[6–8)]



A

Chart 1

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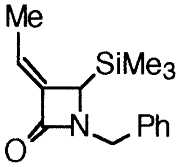
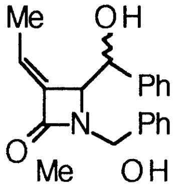
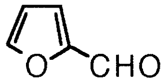
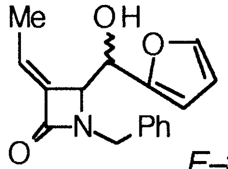
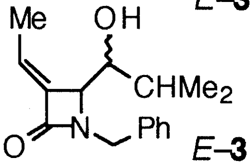
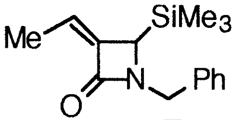
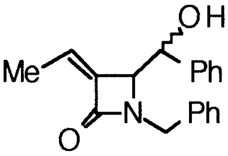
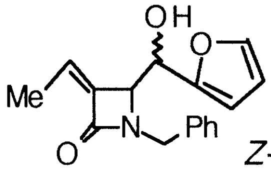
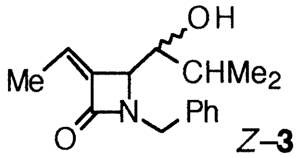
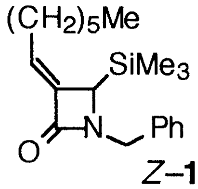
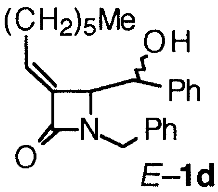
Typical procedure is as follows. To a mixture of **1** (1 mmol) and **2** (3 mmol) in DMF (4 ml) was added Bu_4NF (1 ml, 1 M in THF) which had been dried overnight over molecular sieves.[8] The solution was stirred at room temperature for 24 h, poured into 1N HCl (30 ml), then extracted with ether (20 ml × 3). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was column-chromatographed on silica-gel with AcOEt–hexane (1:5) as an eluent to give **3**. The results are summarized in Table 1.

Table 1. Desilylative α-Hydroxyalkylation of 1

Run	Substrate (**1**)	Aldehyde (**2**)	Product (**3**)	Yield (%)[a]
1	 *Z*–**1a**	PhCHO **2a**	 *E*–**3a**	$74^{b)}$
2	*Z*–**1a**	 **2b**	 *E*–**3b**	$70^{b)}$
3	*Z*–**1a**	Me_2CHCHO **2c**	 *E*–**3c**	$36^{b), c)}$
4	 *E*–**1a**	**2a**	 *Z*–**3a**	$68^{b)}$
5	*E*–**1a**	**2b**	 *Z*–**3b**	$61^{b)}$
6	*E*–**1a**	**2c**	 *Z*–**3c**	$38^{b), c)}$
7	 *Z*–**1b**	**2a**	 *E*–**1d**	$71^{b)}$

a) Isolated yield. b) A mixture (1:1) of diastereoisomers was obtained. c) Reaction was carried out at 60°C.

The desilylative α-hydroxyalkylation of *Z*–**1a,** *E*–**1a** and *Z*–**1b** with aromatic aldehydes **2a** and **2b** took place regioselectively to provide the corresponding 4-(α-hydroxy)alkyl derivatives **3** in high yields (runs 1, 2, 4, 5 and 7). Although the reactions of *Z*–**1a** and *E*–**1a** with aliphatic aldehyde **2c** did not occur at room temperature, the reactions proceeded at 60°C, giving the products *E*–**3c** and *Z*–**3c**, respectively, in fair yields (runs 3 and 6). It should be noted that the stereochemistry of the alkylidene side chain of **1** is kept under the present reaction conditions. For example, the reaction of *E*–**1a** with **2a** gave *Z*–**3a** as the sole isomer, none of the corresponding stereoisomer *E*–**3a** being detected in the ^{1}H-NMR spectrum of crude products.[9]

In summary, electrophilic carbon–carbon bond formation at the C4 position of azetidin-2-ones has been achieved by the reaction of **1** with **2** in the presence of fluoride ion. Since the trimethylsilyl group of **1** can smoothly be displaced not only by nucleophiles such as alcohols, acetic acid and fluoride ion under anodic oxidation conditions[5, 10] but also by electrophiles at the C4 position, substrate **1** will be a versatile synthetic intermediate in the β-lactam chemistry. We are extending this unique carbon–carbon bond formation at the C4 position of azetidin-2-ones to the reactions with other carbon electrophiles.

REFERENCES AND NOTES

1) Georg G. I. (ed.),"The Organic Chemistry of β-Lactams," VCH, New York, 1992.
2) Wild H., in ref. 1, Chapter 2, pp 49–119; and references cited therein.
3) Several radical C–C bond formation reactions at the C4 position of azetidin-2-ones have been reported: Blaszczak L. C., Kenneth H., Halligan N. G., *Tetrahedron Lett.*, **31**, 5693 (1990); Kametani T., Chu S. D., Itoh A., Maeda S., Honda T., *J. Org. Chem.*, **53**, 2683 (1988).
4) To the best of our knowledge, only one example was reported for the electrophilic C–C bond formation at the C4 position of an azetidin-2-one. However, yields and physical data of the products were not recorded in this paper: Nativ C., Ricci A., Taddei M., *Tetrahedron Lett.*, **31**, 2637 (1990).
5) Suda K., Hotoda K., Iemuro F., Takanami T., *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1553.
6) It has recently been reported that α'-amide carbanions ($RCONRCH_2^-$) can be generated by the reaction of an α'-silylated amide ($RCONRCH_2$-$SiMe_3$) with fluoride ion. However, no attempt has ever been made to generate α'-carbanions of lactams from α'-silylated lactams: Cuevas J. C., Snieckus V., *Tetrahedron Lett.*, **30**, 5837 (1989); and references cited therein.
7) The carbanion **A** may also be formed from 3-alkylideneazetidin-2-ones without silyl groups by deprotonation at the C4 position. However, our attempts at such deprotonation reactions with strong bases such as LDA (lithium diisopropylamide) and ^{t}BuLi were unsuccessful.
8) Katrizky A. R., Sengupta S., *Tetrahedron Lett.*, **28**, 5419 (1987).
9) All the products gave satisfactory IR and NMR spectra. For example, ^{1}H-NMR data for *E*–**3a** and *Z*–**3a** are as follows: *E*–**3a** (a 1:1 mixture of diastereoisomers): ($CDCl_3$, 270 MHz) δ 1.03 and 1.47 (each 3/2 H, d, *J* = 7.3 Hz), 3.27 and 3.35 (each 1/2 H, br, OH), 4.21 (1 H, m), 3.70 and 4.72 (each 1/2 H, d, *J* = 15.2 Hz), 4.16 and 4.75 (each 1/2 H, d, *J* = 14.7 Hz), 4.78 (1/2 H, d, *J* = 5.0 Hz), 4.81 (1/2 H, d, *J* = 5.3 Hz), 6.03 (1 H, q, *J* = 7.3, -CH=C), 6.90–7.34 (10 H, m); *Z*–**3a** (a 1:1 mixture of diastereoisomers): ($CDCl_3$, 270 MHz) δ 1.89 (3/2 H, d, *J* = 7.3 Hz), 1.99 (3/2 H, d, *J* = 7.2 Hz), 2.36 and 2.62 (each 1/2 H, br, OH), 3.74 and 4.64 (each 1/2 H, d, *J* = 15.2), 4.41 and 4.75 (each 1/2 H, d, *J* = 14.9 Hz), 3.99 (1/2 H, d, *J* = 5.6 Hz), 4.03 (1/2 H, d, *J* = 7.3 Hz), 4.41 (1/2 H, d, *J* = 7.3 Hz), 4.68 (1/2 H, d, *J* = 5.6 Hz), 4.79 (1/2 H, q, *J* = 7.3 Hz, -CH=C), 5.49 (1/2 H, q, *J* = 7.2 Hz, -CH=C), 6.96–7.35 (10H, m).
10) Suda K., Hotoda K., Aoyagi M., Takanami T., *J. Chem. Soc., Perkin Trans. 1*, **1995**, 1327; Suda K., Hotoda K., Watanabe J., Shiozawa K., Takanami T., *ibid.*, **1992**, 1283.

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