Practical Preparation of 4(*R*)-Allylazetidinones and 4(*R*)-(1-Methylallyl)azetidinones[1]

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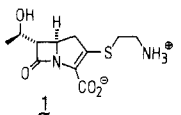
Monocyclic azetidinones **5-7**, which are obtained from 6-aminopenicillanic acid (**3**), were converted into 4(*R*)-allyl- and 4(*R*)-(1-methylallyl)azetidinones **10–12** with allyl- and but-2-enylstannane **8** and **9**. The outcome of the reaction was found to depend on the leaving group in **5–7** and on the reaction conditions. Compounds **10–12** are key intermediates for the synthesis of carbapenem antibiotics.

Since the discovery of thienamycin (**1**)[2] the therapeutic potential of carbapenems has been widely recognized.[3] Because of low fermentation titers and instability of the natural products, synthetic methods had to be developed to provide the necessary amounts of compound required for biological and clinical testing.[4] Pioneering synthetic work was carried out in the laboratories of Merck, Sharp & Dohme where it was shown that azetidinone-4-acetic acids **2** can be efficiently converted into carbapenem antibiotics.[5]



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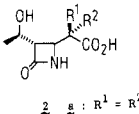
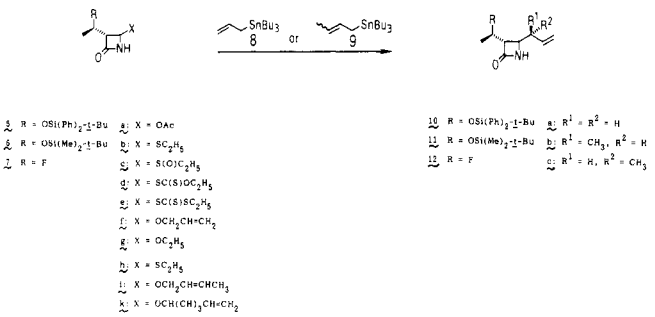


2 a: $R^1 = R^2 = H$; b: $R^1 = CH_3$, $R^2 = H$; c: $R^1 = H$, $R^2 = CH_3$

We have been interested in developing a practical route to **2** starting from 6-aminopenicillanic acid (**3**), which is abundantly available and inexpensive. Efficient stereospecific methods have been developed to convert **3** into methyl 6(*S*)-(hydroxyethyl)penicillanate (**4**)[6] and a number of methods exist to remove the thiazolidine moiety of penicillins to arrive at monocyclic azetidinones of general structure **5**. Many investigations have been reported for substituting X in **5** with various carbon nucleophiles. Organometallic reagents derived from copper,[7] magnesium,[8] or zinc[9] have been used as well as cyanide[10] or other stabilized carbanions[11] like $^-C(COOR)_3$[12] and various enolates.[13] Allylsilanes,[14] silyl enol ether,[15] and ketene silyl

Scheme I



5 a: R = $OSi(Ph)_2$-*t*-Bu; b: R = $OSi(Me)_2$-*t*-Bu; **7**: R = F

a: X = OAc; b: X = SC_2H_5; c: X = $S(O)C_2H_5$; d: X = $SC(S)OC_2H_5$; e: X = $SC(S)SC_2H_5$; f: X = $OCH_2CH{=}CH_2$; g: X = OC_2H_5; h: X = SC_2H_5; i: X = $OCH_2CH{=}CHCH_3$; k: X = $OCH(CH_3)CH{=}CH_2$

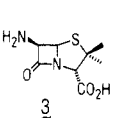
10 R = $OSi(Ph)_2$-*t*-Bu; **11** R = $OSi(Me)_2$-*t*-Bu; **12**: R = F

a: $R^1 = R^2 = H$; b: $R^1 = CH_3$, $R^2 = H$; c: $R^1 = H$, $R^2 = CH_3$

Table I. Reaction of Azetidinones with Stannane 8

starting material	conditn (time, h)	product (yield, %)	recovery of starting material	byproduct (yield, %)
5a	A (20)	**10a** (68)		**5f** (10)
	B (20)	**10a** (12)		**5f** (25)
	C (48)	**10a** (30)		**5f** (6)
	D (20)		80	
5b	A (20)		70	
	B (24)	**10a** (11)	53	
	C (20)		94	
	D (20)		67	
5c	A (48)	**10a** (98)		
	B (24)	**10a** (17)		
	C (24)	**10a** (14)	54	
	D (24)		79	
5d	A (24)	**10a** (96)		
	B (24)	**10a** (72)		
	C (24)	**10a** (62)		
	D (24)		76	
5e	A (24)	**10a** (34)		**5h** (48), **5f** (9)
	B (24)	**10a** (79)		
	C (24)	**10a** (66)		**5h** (30)
	D (48)	**10a** (23)		**5h** (23)
7d	A (8 days)	**12a** (51)	12	**5g** (6)
	C (20)	**12a** (67)		

acetals[16] were successfully used in combination with Lewis acids. The allyl group is of particular versatility since it can readily be converted into either an acetic acid or an acetonyl moiety, thus providing precursors either for thienamycin (**1**) or for carbapenems bearing a (substituted) methyl group in place of the thioether function.[17]



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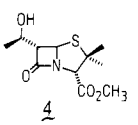

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(1) Dedicated to Prof. Hermann Bretschneider on the occasion of his 80th birthday.

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(17) (a) Hiraoka, T.; Kobayashi, T.; Ishida, N.; Shiozaki, N.; Hirai, K.; Maruyama, H.; Sato, S.; Tamura, C.; Sugawara, S. *Heterocycles* **1984**, *21* 431. (b) Götschi, E. Ger. Pat. 3 201 957, 1982. (c) Hiraoka, T.; Kobayashi, T.; Ishida, N.; Sugawara, S. Ger. Pat. 3 107 854 A1, 1981.

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Table II. Reaction of Azetidinones with Stannane 9

starting material	conditn (time, h)	product (yield, %)	ratio threo: erythro	byproduct (yield, %)
5a	A[a] (20)	**10b,c** (71)	1:1	
5a	A[b] (20)	**10b,c** (75)	1:1	
5c	A (20)	**10b,c** (58)	2:1	
5d	A (20)	**10b,c** (85)	3:2	**5i,k** (10)
5d	B (20)	**10b,c** (30)	10:1	**5g** (20)
6e	C (20)	**11b,c** (42)	5:1	**6h** (27)
7d	A[b] (10 days)	**12b,c** (76)	2:1	
7d	A[a] (3 days)	**12b,c** (<5)		

[a] 0.1 equiv $BF_3{\cdot}Et_2O$ as catalyst. [b] Me_3Si triflate as catalyst.

Since all of the aforementioned methods to introduce carbon substituents into **5** involve either strongly basic or acidic conditions or require low temperature, we are interested in a more versatile and practical method. Allylstannanes are known to transfer the allyl group not only upon catalysis by Lewis acids but also by a radical mechanism.[18] Therefore we decided to undertake a systematic investigation of allylation of **5**, **6**, and **7** by allyl- and but-2-enyltri-*n*-butylstannane **8** and **9** (Scheme I). Preliminary results of our work have already been reported.[19] Subsequently, other reports utilizing allylstannanes have been published.[20] In the present publication we report a detailed study on the influence of the leaving group X in **5** and of the choice of the reaction conditions on the outcome of the allylation reaction.

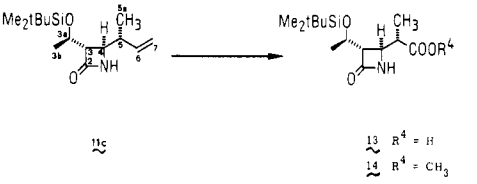
Results

The monocyclic azetidinones **5**, **6**, and **7** were prepared by standard procedures (see Experimental Section). Compounds **5**, **6**, and **7a–e** were reacted either with allyltri-*n*-butylstannane (**8**) or but-2-enyltri-*n*-butylstannane (**9**) under the following conditions: (a) Lewis acid catalysis (trimethylsilyl trifluoromethanesulfonate (Me_3Si triflate) or boron trifluoride etherate) in dichloromethane; (b) catalysis by 2,2′-azobis(isobutyronitrile) (AIBN, toluene, 90 °C); (c) irradiation; (d) heat (toluene, 90 °C). A summary of the results is given in Tables I and II.

Discussion

4-Allylazetidinone **10a** was obtained in almost quantitative yield from **5c** and **5d** in the presence of Me_3Si triflate. When the reaction was performed with AIBN as a catalyst, **10a** could only be obtained from **5d** and **5e** in good yields whereas photoinitiation generally gave disappointing results (in most cases starting material was recovered).[21] Interestingly, it was found that the reaction in some cases took place upon simply heating **5** and **8** or **9** in toluene to 90 °C, yields being best when **5d** and **5e** were used as substrates. When these conditions were applied to the fluoroethyl substrate **7d** the corresponding products **12** were formed within 20 h, whereas the Lewis acid catalyzed reaction was extremely sluggish. Even after eight days and repeated addition of **8** or **9** (2 equiv) and catalyst (1 equiv) on days 2, 4, and 6 starting **7** was not completely consumed. It was also found that in some cases

Scheme II



Me_3Si triflate was a more effective catalyst than boron trifluoride etherate; reaction of **7d** and **9** gave only traces of **12b,c** after eight days whereas a total of 10 equiv of **9** and 7.5 equiv of Me_3Si triflate afforded **12b,c** in 76% yield after the same period. In all cases the allyl or 1-methylallyl group was introduced from the sterically less hindered face of the β-lactam, thus giving products with *R* configuration at the newly created chiral center (this stereochemistry is essential for the antibacterial activity of bicyclic β-lactam antibiotics).

When crotylstannane **9** was used, the products **10b,c**, **11b,c**, and **12b,c** were obtained as diastereomeric mixtures in variable ratios. It is, however, noteworthy that thermal reaction in the presence or absence of AIBN resulted in the predominant formation of the threo isomers **10c**, **11c**, and **12c**, whereas on Lewis acid catalysis the respective erythro isomers **10b**, **11b**, and **12b** were formed in approximately equal amounts. The stereochemistry of the methyl group in **10b,c**, **11b,c**, and **12b,c** was assigned after chromatographic separation of the diastereomers and correlation of the chemical shifts and coupling constants of their ^1H NMR spectra (Table III).[22] Furthermore, the identity of **11c** was proven by converting it into the known acid **13** and its methyl ester[23] **14** (Scheme II). In some reactions byproducts were formed in minor amounts whose structures were established as **5f–k**.[24] The formation of **5g** and **5h** can easily be rationalized by breakdown of the respective leaving group into carbon disulfide and ethanol or ethanethiol and trapping of them by the azetine or azetinium intermediates. The origin of **5f,i,k**, however, is presently not understood. Since neither **8** nor **9** were contaminated with allyl or crotyl alcohol or but-1-en-3-ol these alcohols must have been formed during the reactions from the corresponding tin compounds.

We have also investigated the potential of allyltrimethylsilane (**15**) under our reaction conditions. Lewis acid catalyzed allylation of **5** or **6** by **15** has already been reported previously,[14] and we have found that the use of the silane is limited to these conditions. Allylation of **5** (**6**) neither occurs thermally (with or without AIBN) nor photochemically. These findings are in good agreement with a previous report stating that allylstannanes are more nucleophilic than allylsilanes.[25]

In summary we have shown that 4(*R*)-allyl- and 4(*R*)-(1-methylallyl)azetidinones, which are key intermediates for the synthesis of carbapenem antibiotics, can be obtained in almost quantitative yields from monocyclic degradation products of methyl 6(*S*)-(1-hydroxyethyl) penicillanate and allyl- or but-2-enylstannanes, and that

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(21) We have also tried other leaving groups X (e.g., methylsulfonyl, pthalimido) which yielded no desired products under the conditions used in our studies.
(22) The chemical shifts of H-3, H-4, and H-5 in the ^1H NMR spectra of the erythro series (**10c–12c**) appear somewhat downfield than that of the corresponding threo series (**10b–12b**). This relationship holds for all the subsequent intermediates which we have prepared for the elaboration to the bicyclic carbapenems in which the assignment of stereochemistry was confirmed again by NOE experiments (unpublished results).
(23) Christensen, B. G.; Shih, D. H. European Pat. Appl. 113 103, 1984.
(24) The structure of **5f** was confirmed by an independent synthesis (see Experimental Section). The structural assignment for **5i** and **5k** was based on their ^1H NMR spectra. They both are inseparable mixtures of isomers.
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Table III. ^{1}H NMR Chemical Shifts (Multiplicities and Coupling Constants) of (1-Methylallyl)azetidinones

no.	H_3	H_{3a}	H_4	H_5	H_{3b}	H_{5a}	$H_6/H_7/H_{7'}$	others
12c	2.96 (dddd, J = 19, 7, 2.5, 1.5 Hz)	4.94 (d of quint, J = 48.5, 7 Hz)	3.45 (dd, J = 9, 2.5 Hz)	2.29 (br sextet, J = 7.5 Hz)	1.50 (dd, J = 25, 7 Hz)	1.10 (d, J = 7.5 Hz)	5.00–5.24 (m, 2, H-7/7'), 5.50–5.92 (m, H-6)	5.96 (br, 1)
12b	2.99 (dddd, J = 21.5, 6.5, 2, 1 Hz)	4.94 (d of quint, J = 48.5, 6.5 Hz)	3.53 (dd, J = 7, 2 Hz)	2.38 (br sextet, J = 7 Hz)	1.43 (dd, J = 24.5, 6.5 Hz)	1.09 (d, J = 6.5 Hz)	5.58–5.98 (m, H-6), 5.00–5.25 (m, 2, H-7/7')	6.00 (br, 1)
11c	2.76 (dt, J = 5.5, 2 Hz)	4.18 (dq, J = 6.5, 5.5 Hz)	3.40 (dd, J = 9, 2 Hz)	2.22 (br sextet, J = 7 Hz)	1.23 (d, J = 6.5 Hz)	1.06 (d, J = 7 Hz)	4.98–5.22 (m, 2, H-7/7'), 5.50–5.94 (m, 2, H-6/NH)	0.08 (s, 6), 0.88 (s, 9)
11b	2.82 (ddd, J = 4.5, 2.5, 1 Hz)	4.18 (dq, J = 6, 4.5 Hz)	3.52 (dd, J = 8, 2.5 Hz)	2.33 (br q, J = 7 Hz)	1.17 (d, J = 6 Hz)	1.07 (d, J = 7 Hz)	4.96–5.22 (m, 2, H-7/7'), 5.60–6.00 (m, 2, H-6/NH)	0.07 (s, 6), 0.88 (s, 9)
10c	2.81 (ddd, J = 4.5, 2, 1.5 Hz)	4.30 (dq, J = 7, 4.5 Hz)	3.48 (dd, J = 8, 2 Hz)	2.27 (br sextet, J = 7 Hz)			5.00–5.26 (m, 2, H-7/7'), 5.52–5.94 (m, H-6)	5.88 (br, 1), 0.98–1.18 [m, 15, H-3b/H-5a/ $SiC(CH_3)_3$], 7.34–7.88 [m, 10, $Si(Ph)_2$]
10b	2.87 (ddd, J = 4.0, 2, 1 Hz)	4.28 (dq, J = 6.5, 4 Hz)	3.60 (dd, J = 7.5, 2 Hz)	2.36 (br sextet, J = 7.5 Hz)			4.92–5.20 (m, 2, H-7/7'), 5.50–5.90 (m, H-6)	5.98 (br, 1), 0.98–1.18 [m, 15, H-3b/H-2a/ $SiC(CH_3)_3$], 7.30–7.84 [m, 10, $Si(Ph)_2$]

the use of tin reagents permits a broader variety of substrates and reaction conditions. In addition, we found a distinct preference of but-2-enylstannane to give threo products under thermal reaction conditions.[26] This feature adds to the versatility of tin reagents since the corresponding silicon compounds were not reactive.

Experimental Section

General Methods and Materials. Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 421 spectrometer and are reported in cm^{-1}. Proton magnetic resonance (^{1}H NMR) were obtained either on a Bruker WH-90 DS (90 MHz) or a Bruker WH 250 (250 MHz) spectrometer with tetramethylsilane as an internal standard and chemical shifts are given in parts per million (δ). Mass spectra were recorded with a Varian Mat CH-7 spectrometer. Optical rotation measurements were obtained on a Perkin-Elmer 141 spectrometer. Microanalyses were performed by the Mikroanalytisches Laboratorium of the Inst. f. Phys. Chemie, University of Vienna, Austria. Solvents employed for the reactions were stored over 4Å molecular sieves before use. All commercially obtained chemicals, except for boron trifluoride etherate, were of the highest grade and were used without further purification. Boron trifluoride etherate was first distilled over calcium hydride and stored at −20 °C. All reactions were conducted under an argon atmosphere.

General Procedures for the Reaction of Organostannanes with Substituted Azetidinones. (See Tables I and II for yields of products.) **A. Lewis Acid Catalysis.** The azetidinone (2 mmol) was dissolved in methylene chloride (5–10 mL) and the organostannane (4 mmol) was added, followed by the Lewis acid (0.5 equiv). The resultant mixture was stirred at room temperature. Progress of the reaction was monitored by TLC (HPTLC, silica gel, Merck). Additional amounts of organostannane and/or Lewis acid were added if the progress was too slow. The total amount of reagents used and reaction time are indicated in Tables I and II for the respective substrates. After the reaction, the solvent was removed in vacuo and the residue was taken up in ether, washed once with pH 7 phosphate buffer, and the ether layer was added to a saturated aqueous solution of potassium fluoride.[27] The mixture was stirred vigorously for 30 min, during which tin(IV) fluoride precipitated. Insolubles were removed by filtration, and the layers of the filtrate were separated. The organic phase was dried ($MgSO_4$), concentrated, and then chromatographed on silica gel (Merck).

B. Thermal Reaction in the Presence of AIBN. A mixture of the azetidinone (2 mmol), organostannane (4 mmol), and AIBN (0.1 equiv) in degassed toluene (4 mL) was heated at 90 °C (see Tables I and II for reaction time). After the reaction, toluene was removed in vacuo, and the residue was treated with potassium fluoride solution and worked up as in condition **A**.

C. Thermal Reaction in the Absence of AIBN. The reaction was carried out under identical conditions as in **B**, except no AIBN was added to the reaction mixture.

D. Reaction under Photochemical Initiation. The reaction was performed under irradiation with a Hanau TQ 718 (500-W) high-pressure lamp in a quartz vessel and worked up as before.

Reaction with Allyltrimethylsilane. Reactions of the azetidinones with allylsilane were performed analogously as described in the above conditions by substituting the organostannanes.

Synthesis of Various Azetidinone Substrates. The 4-sulfur-substituted azetidinones were prepared according to literature procedures[28] from the corresponding acetoxy compounds and the appropriate mercaptans. Sulfoxides were obtained from the oxidation of sulfide with *m*-chloroperbenzoic acid (MCPBA) under standard conditions. Acetoxyazetidinone **5a** was prepared from 6(*S*)-[1(*R*)-hydroxyethyl]penicillanic acid methyl ester[5] under analogous conditions which were employed for the synthesis of the corresponding (*tert*-butyldimethylsilyl)oxy derivative.[29] (Fluoroethyl)azetidinone (**7**) was also prepared analogously from the corresponding fluoroethyl penicillanate.[30]

4(*R*)-Acetoxy-3(*R*)-[1(*R*)-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-2-oxoazetidine (5a). This was prepared in 70% overall yield from penicillanate **4** as white crystals: mp 160–164

(26) For the diastereoselectivity of reactions of crotylstannanes with aldimines see Keck, G.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146.

(27) Sometimes precipitation of tin(IV) fluoride started only after addition of a small amount of ethyl acetate.

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(29) Yoshida, A.; Hayashi, T.; Takeda, N.; Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1981**, *29*, 1899.

(30) Mak, C. P.; Fliri, H. Belgium Pat. Appl. 897 351, 1982.

°C; IR (KBr) 1775, 1750, 1230, 1080, 700 cm^{-1}; $[\alpha]^{20}_D$ + 27.5° (*c* 1.0, CH_2Cl_2); NMR ($CDCl_3$) δ 1.02 (s, 9), 1.12 (d, 3, *J* = 6.5 Hz), 2.10 (s, 3), 3.21 (dd, 1, *J* = 4.5, 1 Hz, H-3), 4.20 (dq, 1, *J* = 6.5, 4.5 Hz, H-3a), 5.81 (d, 1, *J* = 1 Hz, H-4), 6.66 (br, 1), 7.30–7.80 (m, 10). Anal. Calcd for $C_{23}H_{29}NO_4Si$: C, 67.12; H, 7.10; N, 3.40. Found: C, 66.91; H, 7.03; N, 3.51.

3(*S*)-[1(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-4(*R*)-(ethylthio)-2-oxoazetidine (5b). This was prepared in 80% yield from **5a** as white crystals: mp 126–128 °C; IR (KBr) 1775, 1140 cm^{-1}; $[\alpha]^{20}_D$ +41.6° (*c* 1.02, CH_2Cl_2); NMR ($CDCl_3$) δ 1.08 (s, 9), 1.11 (d, 3, *J* = Hz), 1.33 (t, 3, *J* = 7.5 Hz), 2.68 (q, 2, *J* = 7.5 Hz), 3.96 (ddd, 1, *J* = 4.5, 2.5, 1 Hz, H-3), 4.31 (dq, 1, *J* = 7, 4.5 hz, H-3a), 4.87 (d, 1, *J* = 2.5 Hz, H-4), 6.33 (br, 1), 7.32–7.84 (m, 10). Anal. Calcd for $C_{23}H_{31}NO_2SSi$: C, 66.78; H, 7.55; N, 3.39. Found: C, 66.71; H, 7.71; N, 3.35.

3(*S*)-[1(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-4(*R*)-(ethylthio)-2-oxoazetidine *S*-Oxide (5c). Oxidation of **5b** with MCPBA provided **5c** in 93% yield as a mixture of isomers: mp 120 °C dec; IR (KBr) 1775, 1760, 1110, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (s, 9), 1.11 (d, *J* = 6.5 Hz, major isomer, CH_3CH_2OSi), 1.15 (d, *J* = 6.5 Hz, minor isomer, CH_3CH_2OSi), 1.34 (t, *J* = 7 Hz, minor isomer, SCH_2CH_3) 1.38 (t, *J* = 7 Hz, major isomer, SCH_2CH_3), 2.50–2.84 (m, 2), 3.40 (dt, = 5.5, 2 Hz, minor isomer, H-3), 3,56 (dt, *J* = 3.5, 2 Hz, major isomer, H-3), 4.26–4.60 (m, 2), 7.12 (br, 1), 7.32–7.80 (m, 10). Anal. Calcd for $C_{23}H_{31}NO_3SSi$: C, 64.30; H, 7.27; N, 3.26. Found: C, 64.05; H, 7.35; N, 3.17.

3(*S*)-[1(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-4(*R*)-[(ethoxythiocarbonyl)thio]-2-oxoazetidine (5d). The compound was obtained in 86% yield as white crystals from **5a**: mp 162–165 °C; IR (KBr) 1775, 1225, 1145, 1110, 1060 cm^{-1}; $[\alpha]^{20}_D$ +83.1° (*c* 1.01, CH_2Cl_2); NMR ($CDCl_3$) δ 1.05 (s, 9), 1.07 (d, 3, *J* = 7 Hz), 1.46 (t, 3, *J* = 7 Hz), 3.20 (ddd, 1, *J* = 5, 2, 0.5 Hz, H-3), 4.32 (dq, 1, *J* = 7.5 Hz, H-3a), 4.69 (q, 2, *J* = 7 Hz), 5.51 (d, *J* = 2 Hz, H-4), 6.60 (br, 1), 7.30–7.80 (m, 10). Anal. Calcd for $C_{24}H_{31}NO_3S_2Si$: C, 60.08; H, 6.59; N, 2.95; S, 13.53. Found: C, 60.33; H, 6.55; N, 2.91; S, 13.23.

3(*S*)-[1(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-4(*R*)-[[(ethylthio)thiocarbonyl]thio]-2-oxoazetidine (5e). This compound was prepared from **5a** in 55% yield as a yellow solid: mp 127–130 °C; IR (KBr) 1775, 1745, 1235, 1145, 1080, 820 cm^{-1}; $[\alpha]^{20}_D$ +124.9° (*c* 1.02, CH_2Cl_2); NMR ($CDCl_3$) δ 1.06 (s, 9), 1.09 (d, 3, *J* = 7 Hz), 1.38 (t, 3, *J* = 7 Hz), 3.24 (ddd, 1, *J* = 5.5, 2.5, 0.5 Hz, H-3), 3.40 (q, 2, *J* = 7 Hz), 4.31 (dq, 1, *J* = 7, 5.5 Hz, H-3a), 5.68 (d, 1, *J* = 2.5 Hz, H-4), 6.68 (br, 1), 7.31–7.80 (m, 10). Anal. Calcd for $C_{24}H_{31}NO_2S_3Si$: C, 58.85; H, 6.40; N, 2.86; S, 19.64. Found: C, 59.24; H, 6.44; N, 2.81; S, 20.06.

4(*R*)-Allyl-3(*S*)-[1(*R*)-[(*tert*-butyldiphenylsilyl)oxy]-ethyl]-2-oxoazetidine (10a): white solid; mp 85–87 °C; IR (KBr) 1760, 1640 (w), 700 cm^{-1}; $[\alpha]^{20}_D$ +8.4° (*c* 0.51, CH_2Cl_2); NMR ($CDCl_3$) δ 1.04 (s, 9), 1.06 (d, 3, *J* = 6.5 Hz), 2.06–2.66 (m, 2), 2.81 (ddd, 1, *J* = 5.5, 2.5, 1.5 Hz, H-3), 3.66 ddd, 1, *J* = 8, 5.5, 2.5 Hz, H-4), 4.22 (br quint, 1, *J* = 6.5 Hz, H-3a), 4.96–5.26 (m, 2), 5.54–6.10 (m, 2), 7.30–7.80 (m, 10). Anal. Calcd for $C_{24}H_{31}NO_2Si$: C, 73.23; H, 7.94; N, 3.56. Found: C, 72.86; H, 7.95; N, 3.54.

4(*R*)-(Allyloxy)-3(*R*)-[1(*R*)-[(*tert*-butyldiphenylsilyl)-oxy]ethyl]-2-oxoazetidine (5f). A mixture of the acetate (0.412 g), allyl alcohol (2.5 mL), and zinc acetate (0.5 g) in benzene (25 mL) was heated at reflux with continuous removal of water (Dean–Stark trap) for 48 h. The resultant mixture was diluted with ethyl acetate and was washed successively with saturated aqueous sodium bicarbonate solution and water. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give the titled compound in quantitative yield. Further recrystallization from pentane/diisopropyl ether gave **5f** as white needles: mp 104–106 °C; IR (KBr) 1765 cm^{-1}; $[\alpha]^{20}_D$ −2.8° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$) δ 1.02 (s, 9), 1.11 (d, 3, *J* = 7 Hz), 3.10 (dd, 1, *J* = 5.5, 1.5 Hz, H-3), 4.00–4.10 (m, 2), 4.22 (dq, 1, *J* = 7, 5 Hz, H-3a), 5.13 (d, 1, *J* = 1.5 Hz, H-4), 5.16–5.26 (m, 2), 5.74–6.18 (m, 1), 6.36 (br, 1), 7.30–7.80 (m, 10); exact mass calcd for $C_{20}H_{22}NO_3Si$ (M^+ − C_4H_9) 352.1363, found 352.1420. Anal. Calcd for $C_{24}H_{31}NO_3Si$: C, 70.38; H, 7.63; N, 3.42. Found: C, 69.75; H, 7.58; N, 3.29. The allyl ether **5f** prepared by this procedure is identical with a sample which was isolated from the reaction of the allyltri-*n*-butyltin and the azetidinones **5**.

3(*R*)-[1(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-4(*R*)-ethoxy-2-oxoazetidine (5g): white solid; mp 135–138 °C; $[\alpha]^{20}_D$ −5.5° (*c* 0.53, $CHCl_3$); NMR ($CDCl_3$) δ 0.96–1.20 (m, 15), 3.07 (dd, 1, *J* = 5.5, 1 Hz, H-3), 3.55 (q, 2, *J* = 7 Hz), 4.21 (dq, 1, *J* = 6.5, 5.5 Hz, H-3a), 5.08 (d, 1, *J* = 1 Hz, H-4), 6.35 (br, 1), 7.32–7.80 (m, 10). Anal. Calcd for $C_{23}H_{33}NO_3Si$: C, 69.13; H, 8.32; N, 3.51. Found: C, 69.00; H, 7.80; N, 3.58.

3(*R*)-(Fluoroethyl)-4(*R*)-[(ethoxythiocarbonyl)thio]-2-oxoazetidine (7d): white solid; mp 82–84 °C dec; $[\alpha]^{20}_D$ +283.8° (*c* 1.03, $CHCl_3$); NMR ($CDCl_3$) δ 1.46 (t, 3, *J* = 7 Hz), 1.50 (dd, 3, *J* = 24, 6.5 Hz), 3.36 (dddd, 1, *J* = 23.5, 5.5, 2.5, 1 Hz, H-3), 4.69 (d, 2, *J* = 7 Hz), 5.12 (ddq, 1, *J* = 48, 6.5, 5.5 Hz, H-3a), 5.50 (d, 1, *J* = 2.5 Hz, H-4), 6.76 (br, 1). Anal. Calcd for $C_8H_{12}FNO_2S_2$: C, 40.48; H, 5.10; N, 5.90. Found: C, 40.58; H, 5.02; N, 5.82.

3(*S*)-[1(*R*)-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4(*R*)-(ethylthio)-2-oxoazetidine (6b): white needles; mp 110–114 °C; $[\alpha]^{20}_D$ +46.5° (*c* 1.02, $CHCl_3$); NMR[31] ($CDCl_3$) δ 0.08 (s, 6), 0.88 (s, 9), 1.24 (d, 3, *J* = 7 Hz), 1.31 (t, 3, *J* = 7.5 Hz), 2.66 (q, 2, *J* = 7.5 Hz), 3.14 (ddd, 1, *J* = 3.5, 2.5, 1 Hz, H-3), 4.27 (dq, 1, *J* = 7, 3.5 Hz, H-3a), 4.86 (d, 1, *J* = 2.5 Hz, H-4), 5.92 (br, 1).

3(*S*)-[1(*R*)-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4(*R*)-[[(ethylthio)thiocarbonyl]thio]-2-oxoazetidine (6e). The titled compound was prepared in quantitative yield from the corresponding acetate[29] **6a** and was used directly without further purification: yellow solid; NMR ($CDCl_3$) δ 0.08 (s, 6), 0.88 (s, 9), 1.22 (d, 3, *J* = 6 Hz), 1.37 (t, 3, *J* = 7 Hz), 3.22 (ddd, 1, *J* = 3, 2, 0.5 Hz, H-3), 3.38 (q, 2, *J* = 7 Hz), 4.31 (dq, 1, *J* = 6, 3 Hz, H-3a), 5.69 (d, 1, *J* = 2 Hz, H-4), 6.60 (br, 1).

4(*R*)-[1-Buten-3(*S*)-yl]-3(*S*)-[1(*R*)-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-2-oxoazetidine (10b): mp 48–52 °C; $[\alpha]^{20}_D$ −10.2° (*c* 0.50, $CHCl_3$); NMR (see Table III).

4(*R*)-[1-Buten-3(*R*)-yl]-3(*S*)-[1(*R*)-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-2-oxoazetidine (10c): mp 107–110 °C; $[\alpha]^{20}_D$ −7.3° (*c* 0.138, $CHCl_3$); exact mass calcd for $C_{21}H_{24}NO_2Si$ (M^+ − C_4H_9) 350.157, found 350.161. Anal. Calcd for $C_{25}H_{33}NO_2Si$: C, 73.66; H, 8.16; N, 3.44. Found: C, 73.00; H, 8.19; N, 3.26. NMR (see Table III).

4(*R*)-[1-Buten-3(*S*)-yl]-3(*S*)-[1(*R*)-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-oxoazetidine (11b): mp 137–139 °C; $[\alpha]^{20}_D$ −14.3° (*c* 0.056, $CHCl_3$); NMR (see Table III); exact mass calcd for $C_{11}H_{20}NO_2Si$ (M^+ − C_4H_9) 226.126, found 226.127.

4(*R*)-[1-Buten-3(*R*)-yl]-3(*S*)-[1(*R*)-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-oxoazetidine (11c): mp 120–123 °C; $[\alpha]^{20}_D$ −13.2° (*c* 0.145, $CHCl_3$); NMR (see Table III). Anal. Calcd for $C_{15}H_{29}NO_2Si$: C, 63.55; H, 10.42; N, 4.94. Found: C, 62.85; H, 10.07; N, 4.91.

4(*R*)-[1-Buten-3(*S*)-yl]-3(*R*)-(fluoroethyl)-2-oxoazetidine (12b): mp 50–53 °C; $[\alpha]^{20}_D$ −16.8° (*c* 0.50, $CHCl_3$); NMR (see Table III); mass spectrum (70 eV), *m/e* (relative intensity) 151 (M^+ − HF, 3), 128 (M^+ − HNCO, 4), 116 (M^+ − C_4H_7, 47), 69 (100); FD-MS ($C_9H_{14}FNO$) 172 (M^+ + 1, 2), 116 (M^+− C_4H_7, 100).

4(*R*)-[1-Buten-3(*R*)-yl]-3(*R*)-(fluoroethyl)-2-oxoazetidine (12c): mp 35–38 °C $[\alpha]^{20}_D$ +25.7° (*c* 0.517, $CHCl_3$); NMR (see Table III). No acceptable microanalysis was obtained for this compound.

4(*R*)-Allyl-3(*R*)-[1(*R*)-fluoroethyl]-2-oxoazetidine (12a): colorless oil; NMR ($CDCl_3$) δ 1.44 (dd, 3, *J* = 23.5, 6.5 Hz), 2.30–2.58 (m, 2), 2.96 (dddd, 1, *J* = 21.5, 6.5, 2, 1 Hz, H-3), 3.74 (td, 1, *J* = 7, 2 Hz, H-4), 4.96 (d quint, 1, *J* = 48.5, 6.5 Hz, H-3a), 5.02–5.30 (m, 2), 5.60–6.04 (m, 1), 6.62 (br, 1); mass spectrum (70 eV), *m/e* (relative intensity) 116 (37), 114 (40), 99 (40), 69 (100); exact mass calcd for C_5H_7FNO (M^+ − C_3H_5) 116.051, found 116.051.

2(*S*)-[(3*S*,4*R*)-3-[1(*R*)-[(*tert*-Butyldimethylsilyl)oxy]-ethyl]-2-oxoazetidin-4-yl]propanoic Acid (13). A mixture of the azetidinone **11c** (260 mg), sodium metaperiodate (880 mg), and ruthenium(III) chloride[32] (5 mg) was stirred vigorously in the solvent mixture CH_3CN–CCl_4–H_2O (2 mL:2 mL:4 mL) for 4 h; it was then diluted with methylene chloride and water, and the layers were separated. After reextraction of the aqueous layer with methylene chloride (2x), the combined organics were dried ($MgSO_4$) and concentrated in vacuo to give a pink solid. This was again taken up in ether and filtered through Celite. The filtrate was concentrated to give the acid **13** as off-white crystals

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(83%): NMR ($CDCl_3$) δ 0.10 (s, 6), 0.90 (s, 9), 1.26 (d, 3, J = 6.5 Hz), 1.30 (d, 3, J = 7 Hz), 2.40-2.76 (m, 1), 2.82 (dm, 1, J = 5.5 Hz, H-3), 3.72 (dd, 1, J = 9, 2 Hz, H-4), 4.22 (quint, 1, J = 6.5 Hz, H-3a), 6.64 (br, 1). Esterification of acid **13** with excess diazomethane gave the crystalline methyl ester **14** which is identical in all respect with that reported by Merck.[23]

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Registry No. **5a**, 97403-52-6; **5b**, 97403-53-7; **5c** (isomer 1), 97403-54-8; **5c** (isomer 2), 97466-02-9; **5d**, 97415-93-5; **5e**, 97465-99-1; **5f**, 97403-55-9; **5g**, 97403-56-0; **5i**, 97403-61-7; **5k**, 97403-62-8; **6a**, 76855-69-1; **6b**, 85768-10-1; **6e**, 96855-25-3; **7d**, 97415-94-6; **8**, 24850-33-7; **9**, 31197-41-8; **10a**, 97403-57-1; **10b**, 97403-58-2; **10c**, 97466-00-7; **11b**, 96613-71-7; **11c**, 96543-02-1; **12a**, 97403-59-3; **12b**, 97403-60-6; **12c**, 97466-01-8; **13**, 97101-07-0; **14**, 87037-96-5; EtSH, 75-08-1.

Reaction of Ketone Enolates with 2,4-Dichloropyrimidine. A Novel Pyrimidine to Pyridine Interconversion[1a]

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Treatment of 2,4-dichloropyrimidine (**1**) with a series of ketone potassium enolates in liquid NH_3 results in a novel ring transformation leading to the formation of 6-(cyanamino)pyridines (**8a-c**). An S_N(ANRORC) mechanism initiated by nucleophilic addition of the enolate to C_6 of **1** is proposed. The pyrimidine–pyridine transformation involves displacement of the N_1–C_2–N_3 portion of pyrimidine with a C–C–N moiety, where the enolate contributes the C–C fragment while NH_3 is shown, using ^{15}N-labeled NH_3, to be the N donor.

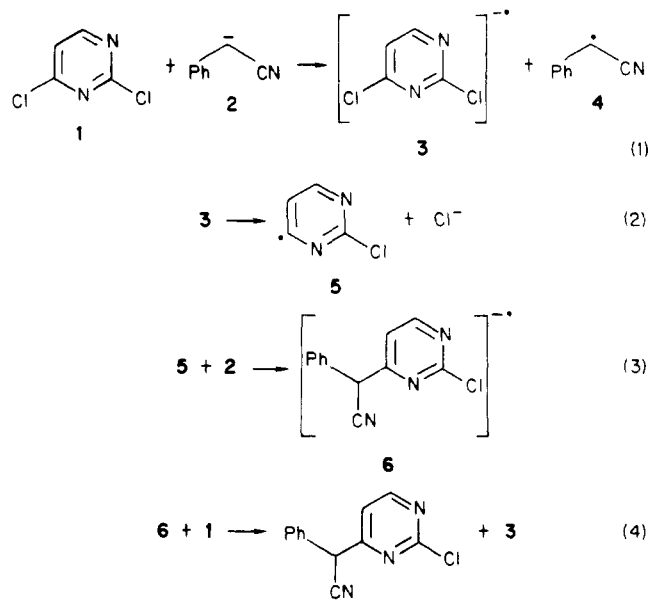
Recent studies of heteroaromatic $S_{RN}1$ reactions in our laboratories[2,3] have demonstrated that certain dihalogenated π-deficient nitrogen heterocycles react with ketone enolates and other carbanionic nucleophiles under photostimulation in liquid NH_3 to yield products resulting from displacement of one or both halogens depending upon the nature of the substrate and nucleophile. For example, photoinduced reaction of 2,4-dichloropyrimidine (**1**) with potassiophenylacetonitrile (**2**) gives exclusively monosubstitution product **7**, resulting from displacement of chlorine from C_4 via the $S_{RN}1$ mechanism shown in Scheme I.[3]

Results and Discussion

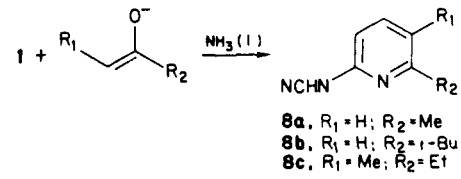
Since carbanion **2** and ketone potassium enolates have previously been observed to react in similar radical-chain fashion with mono- and dihalogenated nitrogen heterocycles,[3,4] we anticipated that photostimulated reactions of substrate **1** with ketone enolates would also lead to regioselective substitution at C_4. However, markedly different and unexpected results were obtained with the potassium enolates of acetone, pinacolone, and 3-pentanone.

Exposure of **1** to excess potassioacetone in liquid NH_3 under near-UV illumination afforded none of the expected mono- or disubstitution product. Instead, 2-(cyanamino)-6-methylpyridine (**8a**)[5] was isolated in 45% yield.

Scheme I



Similarly, (cyanamino)pyridines **8b** (68%) and **8c** (44%) were obtained from reactions of **1** with the potassium enolates of pinacolone and 3-pentanone, respectively.



These pyrimidine–pyridine transformations were not inhibited by di-*tert*-butyl nitroxide (DTBN)[6] and pro-

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