Studies on β-Lactams. XXXIV.[1] α-Carboxy-β-lactams and Derivatives

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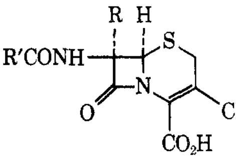
Several 3-chlorocarbonyl-2-azetidinones have been prepared from imines or thioimidates and substituted malonyl chlorides. The β-lactam formation is stereospecific; using pmr techniques, in particular shift reagents, it has been found that the chlorocarbonyl group is cis to the hydrogen or alkylthio group at C-4 of the 2-azetidinone. Dechlorocarbonylation occurs in 3-aryl-substituted members of this series upon treatment with *m*-chloroperoxybenzoic acid leading to the formation of *cis*-3-aryl-2-azetidinones. The chlorocarbonyl group can be converted to an amide side chain *via* the corresponding acid azide and isocyanate. A convenient route is thus available for the stereospecific synthesis of (*E*)-3-substituted 3-amido-2-azetidinones.

Of the various synthetic routes to β-lactams, one that is particularly suited to the preparation of 3-substituted 2-azetidinones is the reaction of an acid chloride with an imine in the presence of a base. We have used azidoacyl chlorides for the preparation of α-azido-β-lactams[2] which can serve as progenitors of α-amino-β-lactams. 6-Epipenicillin methyl ester[3] and a structural isomer of penicillin[4] were synthesized through this approach.

Substituted malonyl chlorides are known[5] to form β-lactams from Schiff bases. We have found the α-chlorocarbonyl-β-lactams so obtained to be valuable intermediates for transformation to other β-lactams.[6] Of particular interest are 3-substituted 3-amido-2-azetidinones[7] (3) in view of the recent discovery[8] of 7-methoxycephalosporins (**1**, R = OMe) antibiotics from *Streptomyces* and the conversion[9] of penicillin to 6-substituted penicillin (2) and 7-substituted cephalosporins (1).



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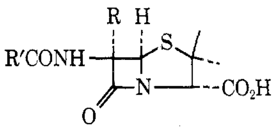

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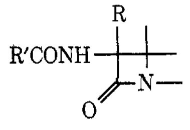

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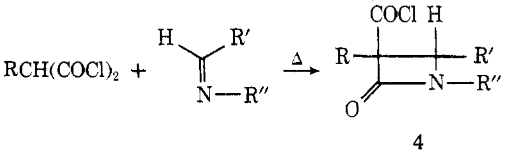
Synthesis of α-Carboxyl-β-lactams. Ziegler and Kleinberg[5] have prepared a number of β-lactams of type 4 in high yield by heating together substituted malonyl chlorides and Schiff base but did not determine the stereochemistry of the products.



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We have found that thioimidates (6) can be condensed with phenylmalonyl chloride to give β-lactams in high yield. Both in the case of Schiff bases and thioimidates the condensation was stereoselective, leading to a single β-lactam instead of a mixture of two possible isomers.

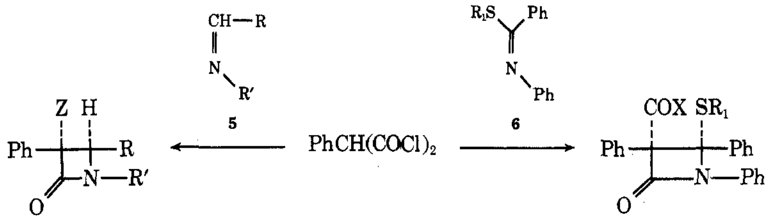
The crude acid chloride β-lactams 7, 24, 25, and 26 were allowed to react with alcohols to obtain crystalline esters (8, 9, 27, 28, 29) in good yield. Attempts to hydrolyze 7 by the method of Ziegler and Kleinberg[5] proved unsuccessful for reasons that are not obvious. The free acid 10 was prepared by the hydrogenolysis of the benzyl ester 9 readily obtained from the acid chloride 7.

Steric Course of β-Lactam Formation. In a previous publication[6] we have assigned the *E* configuration to the β-lactam 7 on the basis that thermal decarboxylation of the corresponding acid 10 led to the *cis*-β-lactam 11. It has been assumed that decarboxylation usually proceeds with retention of configuration.[10] The configuration of the β-lactams derived from thioimidates (6) could not be readily deduced from their pmr spectra, although it was noted that -OMe and -SMe in 27, $-OCH_3$ and $-SCH_2Ph$ in 28, and -OMe and $-SCH_2C_6H_4NO_2$-*p* in 29 were shifted to higher fields than usual.

Joseph-Nathan, *et al.*,[11] have shown that under comparable conditions, an O is much more favorable than an S atom for complexation with a lanthanide shift reagent. Advantage was taken of this difference in complexing ability of the carbomethoxy and the alkylthio substituents with a lanthanide reagent in determining the stereochemistry of the β-lactams **27**, **28**, and **29**. Addition of $Eu(fod)_3$ to β-lactam 27 shifted the $-SCH_3$ and $-OCH_3$ signals downfield; but surprisingly the effect on $-SCH_3$ was much more than on $-OCH_3$, indicating thereby that the Eu atom is located between $-COOCH_3$ and $-SCH_3$ *in this* complex. This could be possible only if both of these groups in 27 are cis to each other. Similar results regarding the cis stereochemistry of SCH_2Ar and CO_2CH_3 groups were obtained when the shift reagent was added to the β-lactams **28** and **29**. Furthermore, the desulfurization of **27**, **28**, or **29** with Raney nickel in acetone generated the β-lactam **8**. It has been shown that the desulfurization reaction proceeds with retention of configuration;[12] therefore the -SR groups at C_4 in β-lactams **27**, **28**, and **29** have the same stereochemistry as C_4H in β-lactam **8**. Consequently, the steric disposition of the -SR substituents in β-lactams **24**–**29** and the C_3-carbomethoxy or COCl groups must be cis to one another. On the basis of the available data it is difficult to make a broad generalization regarding the steric course of this reaction; however, the COCl group of the acid chloride component does appear to exert *an unmistakable influence on the stereochemistry* of the product. In our previous studies[13] on the synthesis of mono- and bicyclic β-lactams from thioimidates and acid chlorides in the presence of triethylamine, we found that the C_4SR and the C-3 substituents were trans to each other in every β-lactam formed by this method.

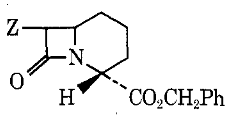
β-Lactam formation through the reaction of malonyl chlorides to thioimidates is equally stereospecific, leading to a cis disposition of the -SR and the COCl group. Taking advantage of this steric course of β-lactam formation, the preparation of a series of *cis*-β-lactams was achieved.

In the course of a study on molecular rearrangement of acid chlorides mediated by *m*-chloroperoxybenzoic acid,[14]



Compd	Z	R	R′
7	COCl	Ph	Ph
8	CO_2Me	Ph	Ph
9	CO_2CH_2Ph	Ph	Ph
10	CO_2H	Ph	Ph
11	H	Ph	Ph
12	COCl	p-C_6H_4OMe	p-C_6H_4Me
13	COCl	p-C_6H_4OMe	β-Naphthyl
14	COCl	Ph	α-Naphthyl
15	H	p-C_6H_4OMe	p-C_6H_4Me
16	H	p-C_6H_4OMe	β-Naphthyl
17	H	Ph	α-Naphthyl
18	CON_3	Ph	Ph
19	NCO	Ph	Ph
20	$NHCO_2CH_2C_6H_4OMe$-p	Ph	Ph
21	$NHCO_2Et$	Ph	Ph
22	$NHCOCH_2OPh$	Ph	Ph
23	$NHCOCH_2Ph$	Ph	Ph

Compd	X	R_1
24	Cl	Me
25	Cl	CH_2Ph
26	Cl	$CH_2C_6H_4NO_2$-p
27	OMe	Me
28	OMe	CH_2Ph
29	OMe	$CH_2C_6H_4NO_2$-p



30, Z = NCO
31, Z = $NHCOCH_2Ph$

it was observed that 3-chlorocarbonyl-2-azetidinones (**7, 12, 13, 14**) produce the *cis*-β-lactams (**11, 15, 16, 17**) in good yield upon treatment with *m*-chloroperoxybenzoic acid and triethylamine at low temperature. This dechlorocarbonylation constitutes a short, stereospecific synthesis of *cis*-β-lactams under mild conditions.

Preparation of α-Substituted α-Amido-β-lactams. The acid chloride β-lactam **7** could be converted easily to the corresponding α-amido derivatives (**20–23**). This provides an alternative pathway for incorporating penicillin side chains in this category of compounds without the intermediacy of an α-amido functionality. Thus, the reaction of the acid chloride β-lactam **7** and the sodium azide afforded the β-lactam **18** with an α-acid azide group. The isocyanate **19** was generated *in situ* from **18** by refluxing it in dry benzene. The reaction of *p*-anisyl alcohol and ethanol with **19** gave the crystalline carbamate **20** and **21**, respectively.

Lowe, *et al.*,[15] were unsuccessful in converting the bicyclic isocyanate **30** directly into its acetamido derivative **31** on treatment with phenylacetic acid. They have, however, achieved this conversion through a multistep reaction.[16] We have found that the isocyanate **19** reacted readily with phenoxyacetic acid in the presence of catalytic amounts of aluminum chloride to provide α-phenyl-α-phenoxyacetamido-β-lactam **22**. Similarly the β-lactam **23** was prepared by the reaction of **19** with phenylacetic acid. Since the Curtius rearrangement is known to proceed with retention of configuration and the acid chloride β-lactam **7** has the *E* configuration (*vide supra*), the entire sequence of reactions leading to α-amido-β-lactams (**20–23**) is stereospecific.

Experimental Section

All melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer using a thin film of Nujol mull, and the nmr spectra were taken on Perkin-Elmer R-12B and Varian A-60A instruments and the chemical shifts are reported in τ units. The mass spectra were obtained on a Hitachi Perkin-Elmer RMU-7 mass spectrometer. The microanalyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany. The yields and other physical constants of the compounds reported in this investigation are given in Table I.

3-Chlorocarbonyl-2-azetidinones were prepared by the method of Ziegler and Kleinberg[5] using phenylmalonyl chloride and the appropriate Schiff bases. These β-lactams were used for further reactions without purification.

1,3,4-Triphenyl-3-carbobenzyloxy-2-azetidinone (9). 1,3,4-Triphenyl-3-chlorocarbonyl-2-azetidinone[5] (**7**, 5 g) was stirred with benzyl alcohol (200 ml) at room temperature for 5 hr. Excess benzyl alcohol was removed under reduced pressure when the product (**9**, 5 g) separated out.

The 3-chlorocarbonyl compounds were similarly converted to the corresponding 3-carbomethoxy derivatives by treating them with anhydrous methanol.

Dechlorocarbonylation of 3-Chlorocarbonyl β-Lactams. 1-(*p*-Tolyl)-3-phenyl-4-(*p*-anisyl)-2-azetidinone (15). *m*-Peroxybenzoic acid (0.6 g, 85%) in CH_2Cl_2 (50 ml) was added to a stirred solution of **12** (1 g) and *triethylamine* (0.3 g) in CH_2Cl_2 at 0°. The stirring was continued overnight and the reaction product was washed with 5% $NaHCO_3$ and water and dried ($MgSO_4$). Removal of the solvent under reduced pressure provided 0.39 g of *cis*-1-(*p*-tolyl)-3-phenyl-4-(*p*-anisyl)-2-azetidinone (**15**) which was purified through column chromatography over Florisil.

By a similar procedure the *cis*-β-lactams **11, 16,** and **17** were prepared from the 3-chlorocarbonyl precursors **7, 13,** and **14**, respectively.

***cis*-1,3,4-Triphenyl-2-azetidinone (11).** *Via* **Thermal Decarboxylation of 10.** The benzyl ester **9** (4 g) in THF (200 ml) and 10% Pd/C (0.5 g) were shaken under hydrogen (45 psi) for 10 hr, the catalyst was filtered off, and the solvent was removed under vacuum at room temperature to furnish 1,3,4-triphenyl-3-carboxy-2-azetidinone (**10**, 3.2 g) which on heating under vacuum at its melting point for 10 min afforded the title compound **11**.

Desulfurization of 4-Alkyl- and 4-Arylthio-2-azetidinones. The β-lactam **27, 28** or **29** (1 g) in anhydrous acetone (150 ml) and Raney nickel (W-7, 10 g) was refluxed with stirring for 8 hr. After cooling, the catalyst was filtered off. Evaporation of the solvent from the filtrate under reduced pressure gave **8**.

1,3,4-Triphenyl-3-azidocarbonyl-2-azetidinone (18). 1,3,4-Triphenyl-3-chlorocarbonyl-2-azetidinone (**7**, 2 g, 0.6 mmol) in anhydrous acetone (50 ml) was added dropwise to a well-stirred solution of sodium azide (1.63 g, 0.6 mmol) in water (5 ml) at 0°. The acid azide β-lactam (**18**) separated out from the reaction mixture, which was stirred for an additional 15 min. The product (1.1 g, 55%) was filtered, dried under vacuum, and used as such for further reactions, ir (Nujol mull) 2128 (azide), 1754 cm^{-1} (β-lactam CO).

1,3,4-Triphenyl-3-(*p*-anisyloxycarbonamido)-2-azetidinone (20). A solution of acid azide β-lactam (**18**, 4.2 g, 0.011 mol) in dry benzene (20 ml) was refluxed for 2 hr. Thereafter *p*-anisyl alcohol (1.7 g, 0.012 mol) and aluminum chloride (15 mg) were added and the mixture was refluxed for another 2 hr. An additional 15-mg quantity of aluminum chloride was added and the refluxing was continued for a further 5 hr. The reaction mixture was then cooled and filtered. The solvent from the filtrate was removed under reduced pressure. Trituration of the residue with dry ether provided **20** (4 g). Similarly the treatment of **18** with ethanol provided **21**.

Table I
Spectral Data of 2-Azetidinones[a]

Compd	Mp, °C	Yield, %	Spectral data
8	162–162[5] (CH_2Cl_2–*n*-hexane)	50–60	Ir 1760 (β-lactam CO), 1725 cm^{-1} (ester CO); nmr τ 2.0–3.0 (m, 15 H), 4.54 (s, 1 H), 6.74 (s, 3 H); M$^+$ at *m/e* 357
9	149–150 (CH_2Cl_2–*n*-hexane)	83	Ir 1745 (β-lactam CO), 1715 cm^{-1} (ester CO); nmr τ 2.1–3.2 (m, 20 H), 4.54 (s, 1 H), 5.3 (s, 2 H); M$^+$ at *m/e* 433
11	183–184[5] (CH_2Cl_2–*n*-hexane)	75	Ir 1742 cm^{-1} (β-lactam CO); nmr τ 2.47–3.0 (m, 15 H), 4.17 (q, 1 H, *J* = 6 Hz), 4.99 (d, 1 H, *J* = 6 Hz)
15	165 (CH_2Cl–*n*-hexane–ether)	41	Ir 1740 cm^{-1} (β-lactam CO); nmr τ 2.6–3.46 (m, 13 H), 4.6, 5.06 (d, *J* = 6 Hz), 6.38 (s, 3 H), 7.72 (s, 3 H); M$^+$ at *m/e* 343
16	175–176 (CH_2Cl_2–ether)	45	Ir 1730 cm^{-1} (β-lactam CO); nmr τ 2.25–3.4 (m, 16 H), 4.48, 4.98 (d, 2 H, *J* = 6 Hz), 6.34 (s, 3 H); M$^+$ at *m/e* 379
17	153 (CH_2Cl_2–*n*-hexane)	43	Ir 1735 cm^{-1} (β-lactam CO); nmr τ 2.05–2.97 (m, 17 H), 4.10, 4.90 (d, 2 H, *J* = 6 Hz); M$^+$ at *m/e* 349
20	128–132 (ether)	73	Ir 3334 (NH), 1760 (β-lactam CO), 1692 cm^{-1} (amide CO); nmr τ 2.26–3.30 (m, 24 H), 4.41 (s, 1H), 5.29 (s, 2 H), 6.20 (s, 3 H)
21	144–145 (ether)	76	Ir 3334 (NH), 1750 (β-lactam CO), 1724 cm^{-1} (carbamate CO); nmr τ 2.15–3.10 (m, 16 H), 4.42 (s, 1 H), 6.64 (q, 2 H, *J* = 7 Hz), 9.1 (t, 3 H, *J* = 7 Hz)
22	173–174 (CH_2Cl_2–*n*-hexane)	68	Ir 3367 (NH), 1754 (β-lactam CO), 1692 cm^{-1} (amide CO); nmr τ 2.26–3.46 (m, 21 H), 4.38 (s, 1 H), 5.9 (s, 2 H)
23	114–115 (CH_2Cl_2–*n*-hexane)	58	Ir 1734 (β-lactam CO), 1692 cm^{-1} (amide CO); nmr τ 2.30–3.32 (m, 21 H), 4.41 (s, 1 H), 6.82 (s, 2 H)
27	179–180 (CH_3OH)	69	Ir 1750 (β-lactam CO), 1715 cm^{-1} (ester CO); nmr τ 1.80–2.80 (m, 15 H), 6.88 (s, 3 H), 8.80 (s, 3 H); M$^+$ at *m/e* 403
28	186–188 (CH_3OH)	65	Ir 1740 (β-lactam CO), 1720 cm^{-1} (ester CO); nmr τ 1.8–3.9 (m, 20 H), 6.9 (s, 3 H), 7.3 (q, 2 H, *J* = 11 Hz); M$^+$ at *m/e* 479
29	155–156 (CH_3OH)	60	Ir 1750 (β-lactam CO), 1760 cm^{-1} (ester CO); nmr τ 1.70–3.5 (m, 19 H), 6.88 (s, 3 H), 7.18 (q, 2 H, *J* = 11 Hz); M$^+$ at *m/e* 524

[a] Satisfactory analyses (±0.4% in C, H, and N) were reported for all new compounds in table with the following exceptions: **16** (C, 0.53% high), **17** (C, 0.43% low; N, 0.49% high); **20** (C, 0.73% low); **28** (C, 0.6% low).

1,3,4-Triphenyl-3-phenoxyacetamido-2-azetidinone (22). Acid azide β-lactam (**18**, 1 g, 2.7 mmol) in benzene (20 ml) was refluxed for 1 hr. Then phenoxyacetic acid (1.26 g, 8.3 mmol) and anhydrous pyridine (2 drops) were added to the reaction mixture and refluxing was continued for another 5 hr. The reaction product was diluted with benzene, washed with sodium bicarbonate solution (5%) and water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the semisolid residue, which upon trituration with dry ether provided **22** (0.8 g).

Using similar reaction conditions as described above, 1 g (2.7 mmol) of acid azide β-lactam **18** and 0.62 g (4.6 mmol) of phenylacetic acid gave 0.7 g of **23**.

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Registry No. **7**, 42834-05-9; **8**, 42834-13-9; **9**, 42834-14-0; **10**, 42834-15-1; **11**, 16141-50-7; **12**, 42834-06-0; **13**, 42834-07-1; **14**, 42834-08-2; **15**, 42834-10-6; **16**, 42834-11-7; **17**, 42834-12-8; **18**, 43210-41-9; **20**, 43210-42-0; **21**, 43210-43-1; **22**, 43210-44-2; **23**, 43210-45-3; **27**, 43210-46-4; **28**, 43210-47-5; **29**, 43210-48-6.

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Acylation of Selected Pyrroles and Tertiary Amides

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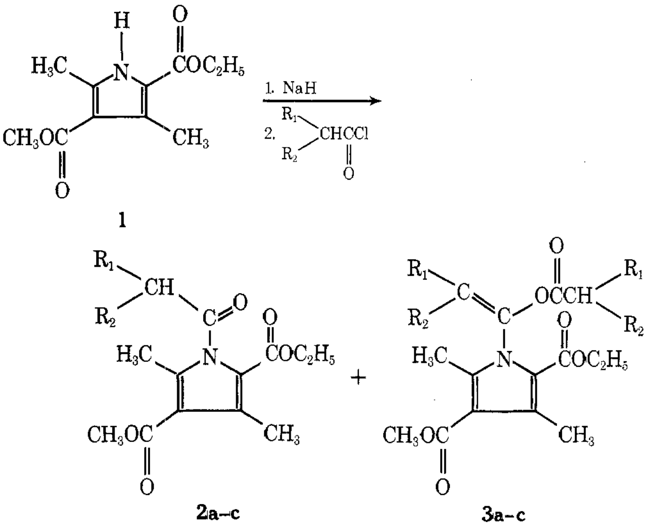
Acylation of 2-ethyl 4-methyl-3,5-dimethylpyrrole-2,4-dicarboxylate (**1**) with acetyl, propionyl, and isobutyryl chlorides gave 1-acylpyrroles **2a–c** and the 1-(1-hydroxyvinyl)pyrrole esters **3a–c** formed by further O-acylation of **2a–c**. Acetylation of *N*-methylacetanilide gave the C-acylation product *N*-methylacetoacetanilide (**7a**), which reacted further to form 3-acetoxy-*N*-methyl-*N*-phenyl-2-butenamide (**8a**); similar C-acetylation products were formed from 9-acetylcarbazole. While C- and O-acetylation products were formed from 1-acetyl-2,5-dimethylpyrrole, the related compounds 1-isobutyryl-2,5-dimethylpyrrole and diethyl 1-acetyl-2,5-dimethylpyrrole-3,4-dicarboxylate afforded only O-acylation products.

A recent report described the preparation of bis acyl derivatives from tetraalkylpyrroles.[1] Our pyrrole work has afforded a second type of bis acylation product, prepared from **1**,[2] and formed by O-acylation of the anion derived from the initially formed monoacyl products **2a–c**.



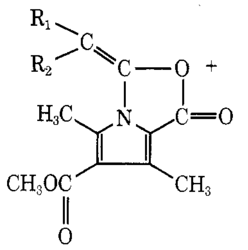
a, $R_1 = R_2 = H$

b, $R_1 = H$; $R_2 = CH_3$

c, $R_1 = R_2 = CH_3$

The mixture of **2a**, **3a**, and **1** obtained when acetyl chloride or acetic anhydride was added to a solution of the sodium salt of **1** in THF was separated into its components by silica gel chromatography. Similar three-component mixtures were formed in the reaction of **1** with propionyl chloride (**2b**, **3b**, and **1**) and isobutyryl chloride (**2c**, **3c**, and **1**), while pivaloyl chloride and benzoyl chloride gave only monoacylation products.[3]

The structures of products **3a–c** were evident from spectral and chemical properties. The nmr spectra showed the absorptions characteristic of the olefinic proton or methyl substituents R_1 and R_2.[4] As expected,[5] the chemical shifts for the remaining substituents in the pyrrole ring were little changed from those in **1** and **2a–c**. The major ions in the mass spectra of **3a–c** were those characteristic of the acyl group and ion **4**.[6] Compound **3a** showed an absorption at 1770 cm^{-1} characteristic for a vinyl ester,[7] with the ring ester groups absorbing at 1680 cm^{-1} as in **1**;[8] compounds **3b** and **3c** showed similar ir carbonyl bands. The uv maxima of **3a–c** in ethanol were at 268 mμ. The absorption is at lower wavelength than in **1** (273 mμ) and has a reduced intensity; both effects have previously been noted for 1-substituted pyrroles.[9,10] Alkaline hydrolysis of **3a–c** regenerated **1**, while refluxing **3c** with excess morpholine gave 4-isobutyrylmorpholine and **1** as the only products.



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Formation of **3** from **2** apparently involves hydrogen abstraction from **2** by the sodium salt of **1**, followed by reaction of the acyl chloride with the resulting anion. Attempts to complete conversion of **1** to **3a** by varying the proportions of reagents in the reaction, or by repeated addition of sodium hydride followed by acetyl chloride to the reaction mixture, were unsuccessful. This appeared to result in part from surface deactivation of the sodium hydride by the acylating reagent. Thus, no hydrogen was evolved when **1** was added to a stirred suspension of sodium hydride in THF containing acetyl chloride; in absence of acetyl chloride, hydrogen evolution was rapid at room temperature.

While compound **2c** did not react with sodium hydride at room temperature,[11] it was converted to the anion using *n*-butyllithium and this was acylated to give **3c**, **5**, and **6**.

Our findings with **1** prompted us to study the acylation