Metallation of N-Substituted β -Lactams. A Method for the Introduction of 3-Substituents into β -Lactams

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N-Alkyl and N-aryl β -lactams yield lithio carbanions upon reaction with lithium diisopropylamide in tetrahydrofuran at -78° . These lithio salts react with a variety of electrophiles (e.g. ketones, esters, reactive alky! halides) to give the 3-substituted derivatives in fair to good yield. The procedure is useful for the preparation of rather complex 3-substituted β -lactams from readily available simple derivatives.

Les ß-lactames N-alkyle et N-aryle donnent des lithiocarbanions en réagissant avec le lithium diisopropylamide dans le tetrahydrofuranne à -78° . Ces sels de lithium réagissent avec divers électrophiles (par exemple cétones, esters, halogénures d'alkyles, réactifs) pour conduire aux dérivés substitués en -3, avec des rendements moyens ou bons. Cette méthode est utile pour la préparation des β -lactames complexes substitués en -3, à partir de dérivés simples, facilement accessibles. [Traduit par le journal]

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A number of authors have recently reported that the reaction of N,N-disubstituted alkyl amides e.g. 1 with strong bases such as NaNH₂ (1, 2), *n*-BuLi (3) or lithio *s*-trithiane (3) leads to carbanions which can be alkylated with a variety of alkyl halides or condensed with carbonyl compounds. e.g. eq. 1.

The problems encountered in the synthesis of complex β -lactams either via cyclization of acyclic precursors or cycloaddition reactions (4), prompted us to investigate the synthesis of a variety of 3-substituted β -lactams from more readily available simple lactams via the carbanion route.

The formation of β -lactam carbanions in the penicillin and cephalosporin series has been investigated by a number of groups (5). In these examples two types of reactions have generally been observed (a) epimerization of the naturally occurring *cis*- β -lactam to the more stable *trans* configuration and (b) β -elimination of the thiolate moiety followed by further rearrangements (Scheme 1).

Several recent reports have indicated some of the synthetic potential of β -lactam carbanions. The first, by Kaiser et al. (6), showed that treatment of the allyldimethylammonium salt 2 with NaH in dimethylformamide-benzene resulted in the intramolecular migration of the allyl group from nitrogen to carbon thereby forming 3 (eq. 2).

More pertinent to the work discussed in this paper are the results of Böhme et al. (7) who were able to transform methyl N-benzylidene-6-aminopenicillanate (4) into a mixture of the epimeric-6-methyl derivatives 5 and 6 upon reaction with CH₃I/NaH in dimethoxyethane at 0° (eq. 3). In this case the ease of carbanion formation is undoubtedly due in large part to the additional stabilization afforded by the neighboring N=CHPh group. A similar reaction was also carried out on the analogous cephalosporin derivative.

More recently, Firestone and coworkers (8) have shown that the imine prepared from 6aminopenicillanic acid benzyl ester and p-



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nitrobenzaldehyde readily yielded a carbanion upon treatment with phenyllithium in tetrahydrofuran at -78° . Alkylation of this carbanion with methyl and ethyl iodide gave the 6α alkylated isomers.

We have found that simple monocyclic N-methyl² or N-phenyl β -lactams readily form lithio derivatives upon addition to an equimolar amount of lithium diisopropylamide in tetra-hydrofuran at -78° . These species are reasonably stable at -78° and react readily with a variety of electrophiles to yield the 3-substituted derivatives in fair to good yield (eq. 4, Table 1).

Thus the lithio salt 7*a* reacted with acetone or methyl iodide to afford the products 11 and 12 in 80 and 59% yield respectively. The i.r. spectrum of each product showed a strong band in the 1730–1750 cm⁻¹ region which confirmed that the β -lactam ring had been retained (9). In the n.m.r. spectrum of each product the coupling between the two remaining ring protons was <2.5 Hz, indicative of the *trans*-configuration (10). No evidence of the presence of the *cis* isomers of **11** and **12** was detected in the n.m.r. spectra of the total crude products. The other spectroscopic features were as expected and are recorded in the Experimental. The lithio salts of the β -lactams **9** and **10** also yielded only one product on reaction with the various electrophiles. These were also shown by n.m.r. to have the *trans* configuration. Not unexpectedly, diastereomeric mixtures were obtained from the lithio salt of **8**. No attempts were made to separate these diastereomers.

The 3-methyl- β -lactam 12 also yielded a lithio derivative (12*a*) which was trapped with benzophenone to give 13 in a 30% yield. When 12*a* was quenched with H₂O, 12 was regen-



²Methylation of N-unsubstituted β -lactams was carried out by dissolving such lactams in excess CH₃I at 0–10° and slowly adding I equiv dry, powdered KOH. The yield of N-methylated β -lactams was generally over 80%. This alkylation procedure was also successful with other reactive halides such as benzyl or allyl bromide, but not with ethyl bromide or isopropyl iodide. In the latter experiments polymerization of the β -lactam occurred.

[2]

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3197

R

CH₃

7 CH₃ 8

9

10 Ph





н



TABLE 1. Introduction of a 3-substituent into 2-azetidinones

357

Lithio salt	Electrophile Acetone	Yield %	
		80	(11)
7 a	Methyl iodide	59	(12)
7 a	Methyl benzoate	28	(14)
	-	50	(15)
8 a	Acetone	77	
8 a	Benzophenone	75	
8 a	<i>n</i> -Butylbromide	0	
9 a	Benzophenone	50	
10 a	Cyclohexanone	41	
10a	Acetone	58	
10 a	Iodine	29	
10 a	Methyl benzoate	61	
1 2 a	Benzophenone	30	(13)



erated; no evidence of isomerization to the cis isomer was detected by n.m.r.

Reaction of 7a with methyl benzoate led to the formation of the phenacyl lactam 14 (i.r. 1750 and 1680 cm⁻¹) in 28% yield. The trans stereochemistry is assigned by analogy with 11 and 12 but could not be verified by n.m.r. In addition to the above material, a second product was obtained in 50% yield to which is

tentatively assigned the dilactam structure 15. The material had a broad m.p. (128-151°) and is probably a mixture of diastereomers. The i.r. spectrum of 15 showed bands at 3580 and 3400 (free and bonded OH), 1740 (C=O), 988, and 930 cm⁻¹ (terminal vinyl). N.m.r. bands occurred at δ 2.4–2.8 (three sharp lines, total 6H, due to the NCH₃ group of the various diastereomers), 3.1 (s, 1H, OH), 3.5-4.0 (m, 4H, ring H), 4.8-6.0 (m, 6H, vinyl), and 7.2-7.7 (m, 5H, aromatic).



In addition to the adducts derived from the lithio salt of 10a, we generally observed the formation of a small amount of bi-product which was identified as 16 (see Experimental for spectroscopic data). The yield of 16 can be increased to about 27% by allowing a solution of 10a to warm to room temperature in the absence of a trapping agent. Its mode of formation is suggested in eq. 5. Products analogous to 16 were not observed in the reaction of the lithio salts of the N-alkyl- β -lactams.



Experimental

N.m.r. spectra were recorded as CHCl₃ solutions using Varian T-60 and HA-100 spectrometers; peak positions are quoted in δ units. I.r. spectra were recorded in CHCl₃

solution, unless otherwise indicated, on a Beckman IR-20 spectrophotometer. Melting points and boiling points are uncorrected. For the sake of unambiguous designations, the 2-azetidinone nomenclature is used in this part of the paper.

1,4-Diphenyl-2-azetidinone

This 2-azetidinone was prepared by the method of Gilman and Speeter (11) as found in ref. 12.

4-Vinyl-2-azetidinone and 2-Methyl-4-vinyl-2-azetidinone

These 2-azetidinones were prepared by the method of Moriconi and Meyer (13) except that reduction of the 1-chlorosulfonyl-2-azetidinones was carried out with sodium sulfite (14).

4-Phenyl-2-azetidinone

This compound was obtained from the reaction of styrene and chlorosulfonyl isocyanate in methylene chloride followed by sodium sulfite reduction of the crude *N*-chlorosulfonyl β -lactam; m.p. 106–108°; lit. m.p. 108–109° (15).

N-Methylation of 2-Azetidinones. General Procedure

The 2-azetidinone was mixed with an excess of methyl iodide. The mixture was cooled to 0° and 1 equiv of freshly powdered dry potassium hydroxide was added with stirring. The mixture was then stirred at the temperatures and for the times indicated. The work-up consisted of adding methylene chloride and filtering the mixture. The methylene chloride was dried over magnesium sulfate and evaporated to give almost pure products.

I-Methyl-4-vinyl-2-azetidinone

4-Vinyl-2-azetidinone (4.01 g, 41 mmol) and 11.4 g of methyl iodide were stirred with 2.36 g of potassium hydroxide. Work-up gave 3.8 g (83%) of product, b.p. $34-35^{\circ}/0.35$ mm. The n.m.r. spectrum showed peaks at δ 2.75 (s, 3H), 2.45-3.39 (m, 2H), 3.78-4.09 (m, 1H), and 5.12-6.18 (m, 3H). The i.r. spectrum showed bands at 1735 (s), 1410 (m), 1390 (m), 990 (m), and 930 (m). The mass spectrum gave a molecular ion at m/e 111.

1,4-Dimethyl-4-vinyl-2-azetidinone

4-Methyl-4-vinyl-2-azetidinone (2.65 g, 23.8 mmol) and 6.8 g (48 mmol) of methyl iodide were stirred with 1.34 g (24 mmol) of potassium hydroxide for 10 min. Work-up gave 2.78 g of yellow oil (90%) which was pure by n.m.r. The product was distilled and gave a colorless liquid b.p. $40-50^{\circ}/0.35$ mm. The n.m.r. spectrum indicated peaks at δ 1.75 (s, 3H), 2.69 (s, 3H), 2.81 (s, 2H), and 5.00–6.21 (m, 3H). The i.r. spectrum showed bands at 1735 (s), 1410 (m), 1390 (m), 995 (m), and 930 (m) cm⁻¹.

1-Methyl-4-phenyl-2-azetidinone

To a solution of 4-phenyl-2-azetidinone (7.5 g, 51 mmol) in 60 ml CH₃I was added slowly 3.1 g of powdered KOH. The reaction mixture was stirred overnight at room temperature. The precipitate was filtered and washed with 50 ml of CH₂Cl₂. The solvents were evaporated and the product distilled. The yield of methylated β -lactam, b.p. 86-90°/0.2 mm, was 6.4 g (78%). The i.r. spectrum showed the β -lactam carbonyl at 1740 cm⁻¹. The n.m.r. spectrum showed the following peaks: δ 2.72 (s, 3H), 2.79 (d of d, J = 16, 2.5 Hz, 1H), 3.04 (d of d, J = 16 Hz, 4.5H), 4.47 (d of d, J = 4.5 Hz, 2.5), and 7.32 (s, 5H). The mass spectrum showed the parent peak at m/e = 161.

Formation of 3-Substituted-2-azetidinones. General Procedure

To a tetrahydrofuran solution of 1.1 equiv of diisopropylamine under nitrogen atmosphere at -78° was added 1.0-1.1 equiv of *n*-butyllithium (Foote Mineral Co., 1.6 *M* in hexane). After 5 min a tetrahydrofuran solution of the 2azetidinone which had been cooled to -78° was added to the first solution and this was stirred for 0.5-1.5 min. A selected electrophile was then added, either neat if liquid, or as a tetrahydrofuran solution if solid. The reaction was stirred at -78° for the time specified. The solution was then poured into water and the aqueous phase saturated with sodium chloride. The products were extracted with methylene chloride and dried over magnesium sulfate. The products were usually purified by preparative t.l.c. or column chromatography. Yields refer to purified materials.

Formation of 3-Derivatives of 1-Methyl-4-vinyl-2azetidinone

(a) Acetone Derivative (11)

To a solution of 3.88 mmol of the lithio salt of 7 was added 3 ml (40 mmol) of acetone. The reaction mixture was stirred for 5 min at -78° . Work-up gave 704 mg of a colorless oil from which 522 mg (80%) of 11 was isolated as a pale yellow oil by preparative t.l.c. using 5% CH₃OH in CHCl₃ as eluent. The i.r. spectrum showed strong bands at 3440 and 1730 cm⁻¹; n.m.r. peaks occurred at δ 1.24 (s, 3H), 1.43 (s, 3H), 2.60 (s, 1H, O—H), 2.75 (s, 3H), 2.88 (d, J=2.0 Hz, 1H), 3.90 (d of d, J=2.0 and 8.0 Hz, 1H), and 5.2–6.1 (m, 3H).

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.79; H, 8.97; N, 8.40.

(b) 3-Methyl Derivative (12)

A solution of 8.5 mmol of 7*a* and 3 ml (50 mmol) of methyl iodide was allowed to react for 10 min. Work-up followed by purification by preparative t.l.c. gave 630 mg (59%) of **12** as an oil. The n.m.r. spectrum showed peaks at δ 1.30 (d, J=7.5 Hz, 3H), 2.73 (s, 3H), 2.66–2.94 (m, 1H), 3.50 (d of d, J = 8.0 and 2.0 Hz, 1H), 5.10–6.10 (m, 3H).

Anal. Calcd. for $C_7H_{11}NO: C$, 67.17; H, 8.86; N, 11.19. Found: C, 66.89; H, 9.01; N, 11.02.

(c) Benzoyl Derivatives (14 and 15)

From the reaction of 4.1 mmol of 7*a* and 550 mg (4.5 mmol) of methyl benzoate was obtained 862 mg of crude product. Preparative t.l.c. gave two products on development with 5% methanol in chloroform. The upper fraction was obtained as a yellowish solid, 240 mg (28%), and was recrystallized from ether-pentane to give white needles, m.p. $66.5-67.5^{\circ}$. The i.r. spectrum showed strong bands at 1750 and 1680 cm⁻¹; the n.m.r. spectrum showed peaks at δ 2.80 (s, 3H), 4.50-4.70 (m, 2H), 5.24-6.00 (m, 3H), 7.24-7.29 (m, 3H), and 7.91-8.24 (m, 2H).

Anal. Calcd. for C₁₃H₁₃NO₂: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.48; H, 6.01; N, 6.51.

A lower fraction was extracted from the plate to yield 336 mg (50%) of white solid, m.p. $128-151^{\circ}$ (methylene chloride-ether-pentane) to which we have assigned structure **15**. The i.r. spectrum showed bands at 3580 (w), 3400 (b), 1740 (s), 1542 (w), 988 (m), and 930 (m) cm⁻¹. The n.m.r. spectrum is described in the text.

Anal. Calcd. for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.95; H, 6.80; N, 8.60.

Formation of 3-Derivatives of 1,4-Dimethyl-4-vinyl-2-

(a) Acetone Derivative

azetidinone

A solution of the lithio salt **8***a*, prepared from 334 mg (2.7 mmol) of **8**, was reacted with 3 ml of acetone for 5 min, at -78° . Work-up gave 538 mg of colorless oil which after purification by preparative t.l.c. gave 377 mg (77%) of white solid, m.p. 64.5–70.5° (methylene chloride–ether–pentane). The n.m.r. spectrum showed peaks at δ 1.16–1.75 (m, 9H), 2.42–3.09 (m, 5H), and 5.00–6.45 (m, 3H). The i.r. spectrum showed bands at 3580 (m), 3440 (b), 2980 (s), 1730 (s), 1375 (s), 999 (m), and 925 (m).

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.45; H, 9.16; N, 7.62.

(b) Benzophenone Derivative

To a solution of 3.0 mmol of the lithio salt **8***a* was added 550 mg (3.0 mmol) of benzophenone. The reaction was worked-up after 5 min to yield 850 mg of crude product. Column chromatography (silica gel, chloroform-methanol) gave 683 mg (75%) of adduct as a mixture of diastereomers, m.p. $147-152^{\circ}$ (methylene chloride-ether). The n.m.r. spectrum showed peaks at δ 1.05 and 1.37 (two singlets, 3H), 2.66 and 2.67 (2 singlets, 3H), 2.81 and 3.03 (two singlets, 1H), 4.23 (s, 1H, exchangeable with D₂O), 4.83-5.93 (m, 3H), and 7.00-7.80 (m, 10 H). The i.r. spectrum showed bands at 3420 (b), 1730 (s), 980 (w), and 920 (w) cm⁻¹.

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.03; H, 6.96; N, 4.53.

Benzophenone Adduct of I-Methyl-4-phenyl-2-azetidinone

A solution of the lithio salt 9a was prepared by reacting 371 mg (2.3 mmol) of 9 with 2.5 mmol of lithium diisopropylamide for 1 min. Benzophenone (420 mg, 2.6 mmol) was then added and the reaction mixture stirred for 6 min. Work-up gave 750 mg of an orange solid from which 390 mg (50%) of adduct was obtained as a white powder, m.p. 216-217° (methylene chloride-ether). The i.r. spectrum had bands at 3560 (w), 3360 (broad), and 1730 (s) cm⁻¹. The n.m.r. peaks occurred at 2.75 (s, 3H), 4.00 (broad singlet, 1H), 4.33 (d, J=2.0 Hz, 1H), and 7.00-7.66 (m, 15 H). The OH absorption could not be seen in the n.m.r.

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.32; H, 6.01; N, 4.07.

Benzophenone Derivative of 1,3-Dimethyl-4-vinyl-2azetidinone

A solution of 220 mg (1.76 mmol) of **12** was added to 1.1 equiv of lithium diisopropylamide and 320 mg (1.0 equiv) of benzophenone was added after 1.25 min. The reaction was stirred for a further 10 min. Work-up gave 558 mg of crude product which was recrystallized to give 162 mg (30%) of pure **13**, m.p. 171-172.5° (methylene chloride – ether-pentane). The i.r. spectrum showed bands at 3600 (w), 3460 (broad), 1735 (s), 1020 (w), and 925 (w) cm⁻¹. The n.m.r. showed peaks at δ 1.30 (s, 3H), 2.46 (s, 3H), 3.36 (broad singlet, 1H), 3.90 (d, J=7 Hz, 1H), 5.03-6.06 (m, 3H), and 7.12–7.69 (m, 10 H).

The mass spectrum of the compound indicated the parent peak at m/e = 307, calcd for $C_{21}H_{20}NO_2 = 307$.

3-Derivatives of 1,4-Diphenyl-2-azetidinone

(a) 3-Iodo Derivative

A solution of 2.23 g (0.01 mol) of 2-azetidinone and 1.1

equiv of lithium diisopropylamide was stirred for 3 min. Iodide (2.54 g. 1 equiv was added; the reaction was stirred for a further 30 min. The work-up was carried out as usual except that the aqueous layer was saturated with sodium sulfite. Column chromatography (pentane-ether) of the crude product yielded 1.022 g grey solid (29%), m.p. 106.5-108° (ether-pentane). The n.m.r. spectrum indicated peaks at δ 4.72 (d. J = 2.0 Hz, 1H), 5.14 (d. J = 2.0 Hz, 1H), 7.04-7.47 (m, 10 H). The i.r. spectrum showed bands at 1755 (s), 1600 (m), and 1374 (m) cm⁻¹. The mass spectrum of the compound indicated the parent peak at m/e = 349. Since the compound tended to decompose, it was not analyzed.

(b) Cyclohexanone Derivative

To a solution of 3.14 mmol of the lithio salt of 1,4diphenyl-2-azetidinone was added cyclohexanone (310 mg, 3.14 mmol) and the reaction stirred for 10 min. Column chromatography of the 700 mg of crude product gave 416 mg (41%) of pale yellow solid. Recrystallization from methylene chloride – ether – pentane gave white needles, m.p. 163–164°. The i.r. spectrum showed bands at 3580 (w), 3430 (b), 2940 (s), 1735 (s), 1600 (m), 1495 (m), 1380 (m), and 1145 (m) cm⁻¹. The n.m.r. spectrum showed peaks at δ 1.06–2.10 (m, 11 H), 3.16 (d, J = 2.5 Hz, 1H), 5.06 (d, J = 2.5 Hz, 1H), and 7.00–7.48 (m, 10H).

Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H. 7.21. Found C, 78.35; H, 7.21.

(c) Acetone Derivative

1,4-Diphenyl-2-azetidinone (3.97 mmol) was stirred with 1.0 equiv of lithium diisopropylamide for 30 s and 3 ml (10 equiv) of acetone was added. The reaction was stirred for 10 min. Work-up gave 1.18 g of yellow solid. Column chromatography yielded 643 mg (58%) white solid, m.p. 148-149.5° (methylene chloride – ether–pentane). The n.m.r. spectrum showed peaks at 1.32 and 1.43 (two singlets. 6H), 1.87 (s, 1H), 2.10 (d, J = 2.5 Hz, 1H). 5.00 (d, J = 2.5 Hz, 1H), and 7.00–7.45 (m, 10H). The i.r. spectrum showed bands at 3580 (w), 3460 (b), 1725 (s), 1600 (m), 1350 (m), and 1375 (m) cm⁻¹.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.97. Found: C, 76.25; H, 6.77; N, 4.90.

(d) Benzoyl Derivative

1,4-Diphenyl-2-azetidinone (1.22 g, 5.49 mmol) was stirred with 1.05 equiv of lithium diisopropylamide for 30 s and 1 equiv of methyl benzoate was added. After 10 min the reaction was worked-up to give 1.85 g of yellow solid. Column chromatography yielded 1.1 g (61%) of white solid, m.p. 133-136° (methylene chloride-ether-pentane). The n.m.r. spectrum showed peaks at δ 4.80 (d, J = 2.0 Hz, 1H), 5.75 (d, J = 2.0 Hz, 1H), 6.95-7.61 (m, 13 H), 8.05-8.25 (m, 2H). The i.r. spectrum showed bands at 1740 (s), 1682 (s), and 1600 (m) cm⁻¹.

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.24; N, 4.28. Found: C, 80.48; H, 5.47; N, 4.20.

Decomposition of the Lithio Salt of 1,4-Diphenyl-2azetidinone (10a)

To a solution of 1.1 equiv of lithium diisopropylamide was added 2.80 mmol of 2-azetidinone and the solution allowed to warm to room temperature over 20 min. Workup yielded 630 mg of crude material which was recrystallized from methylene chloride – ether to give 167 mg (27%) of **17** as a white solid, m.p. $182-183^{\circ}$. The i.r. spectrum (KBr pellet) showed bands at 3380 (w), 1740 (s), 1710 (s), 1600 (m), 1490 (m), 1360 (m), 750 (m), and 690 (m) cm⁻¹. The n.m.r. spectrum (DMSO- d_6) showed peaks at 2.78-3.48 (m, 2H), 4.57 (d, J = 2.5 Hz, 1H), 4.72-5.08 (m, 1H), 5.42 (d, J = 2.5 Hz, 1H), 6.06 (d, J = 7.5 Hz, 1H), 6.48 (d, J = 6.5 Hz, 2H), 6.82-7.60 (m, 18 H).

Anal. Calcd. for $C_{30}H_{26}N_2O_2$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.58; H, 5.95; N, 6.25.

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