Dimetallation of β-Lactams. Introduction of 3-Substituents in *N*-Unsubstituted β-Lactams

T. DURST, R. VAN DEN ELZEN, AND R. LEGAULT
Department of Chemistry, University of Ottawa, Ottawa, Canada K1N 6N5

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β-Lactams, unsubstituted in the 1 and 3 position react with 2 equiv. of *n*-butyllithium in THF at 0° within 1 h to form 1,3-dilithio salts. The dilithio salts react with various electrophiles (ketones, alkyl halides, I_2) to give β-lactams substituted in the 3 position.

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Les β-lactams, non-substitués dans leurs position 1 et 3, réagissent en moins d'une heure avec deux équivalents de *n*-butyllithium dans le THF à 0° pour former les sels dilithiés en position 1 et 3. Les sels dilithiés réagissent avec divers électrophiles (les cétones, les halogénures d'alkyle et I_2) pour fournir des β-lactams substitués en position 3. [Traduit par le journal]

Recently we reported on the metallation of *N*-substituted β-lactams at the 3 position upon treatment of lactams such as **1** (R = Alkyl or Aryl) with lithium diisopropylamide and on the synthetic utility of the metallated species **2** for the introduction of substituents into the 3 position into such lactams (see eq. 1) (1*a*). Closely related to the above has been the considerable use over the past few years of carbanionic intermediates at position 6 in penicillins (1*b*) and 7 in cephalosporins (1*b*) for the introduction of a variety of substituents into these positions (eq. 2).

[1] 

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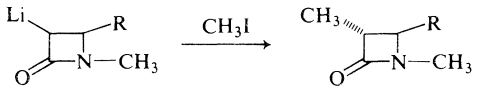
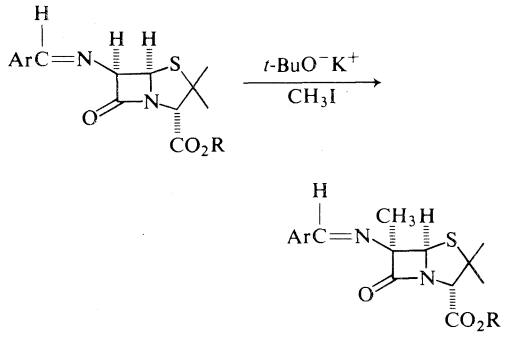
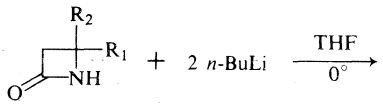


2 **3**

[2] 

We would now like to report an extension of the above results to the formation of *N*,*C*-3-dimetallated β-lactams such as **5**. Addition of various electrophiles such as alkyl halides, carbonyl compounds, and iodine results, as expected, in reaction only at C-3 and thus provides a relatively simple method for the introduction of substituents at that position in simple *N*-unsubstituted β-lactams.

[3] 

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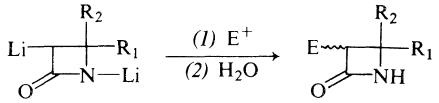
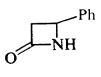


5 **6**

a R_1 = Ph; R_2 = H
b R_1 = Vinyl; R_2 = H
c R_1 = Vinyl; R_2 = CH_3
d R_1 = CH_2CH_3; R_2 = H

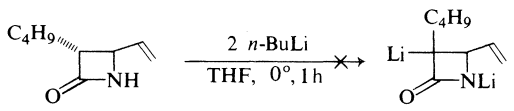
The expectation that β-lactams might form stable dianions was based on the observation by Hauser and co-workers (2) that acetanilide undergoes dimetallation on reaction with *n*-butyllithium in tetrahydrofuran at 0°. When the β-lactams **4***a–d* were reacted with 2 equiv. of *n*-BuLi in THF at 0° for 30–60 min, dimetallation occurred in up to 90% yield as shown by subsequent trapping experiments (see Table 1).

TABLE 1. Introduction of substituents into position 3 of β-lactams

β-Lactam	Electrophile	Yield (%) of 3-substituted product
 **4a**	Acetone	55
	Methyl iodide	53
	n-Butyl bromide	66
	Iodine	16
 **4b**	Benzophenone	88
	Cyclohexanone	55
	n-Butyl bromide	77
	Isopropyl bromide	45
 **4c**	Benzophenone	57
 **4d**	Benzophenone	65
	n-Butyl bromide	65

The structures of the products followed from spectroscopic and analytic data. The i.r. spectrum of each product showed bands in the regions 3300–3400 and 1730–1760 cm^{-1} thus confirming that the *N*-unsubstituted β-lactam structure had been retained. In contrast to the reaction of the monoanion **2** with electrophiles which produced only *trans*-3,4-substituted β-lactams (1), the reaction of the dianions **5** with the same electrophiles usually produced mixtures, the *trans–cis* ratio varying from about 3:1 to 10:1. The formation of the two isomers from **4***a*, *b*, *d* was confirmed by the n.m.r. spectra of the crude products. Inspection of the signal due to the C-4 proton revealed two areas of absorption, one showing a coupling constant of ~2 Hz, the other a J = 4–5 Hz with the remaining proton on C-3. These were assigned to the *trans* and *cis* isomers, respectively (3). For the products obtained from **5***c* the isomeric mixture was evident from the appearance of two singlets due to the remaining proton at C-3.

Dimetallation of the 3-alkylated β-lactam **7** under conditions which resulted in metallation of **4** was not successful and the starting material was recovered. This result was not altogether unexpected in view of the well-known decrease in acidity in going from a secondary to a tertiary hydrogen.



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Experimental

Melting points were taken on a Thomas Hoover apparatus and are uncorrected. Infrared spectra were obtained as films for liquids and in $CHCl_3$ solution for solids on a Beckman IR-20A Spectrophotometer; n.m.r. spectra were obtained using Varian HA-100 and T-60 Spectrometers; peak positions are reported in δ units. All reactions involving alkyllithiums were carried out using freshly distilled tetrahydrofuran (THF) and under N_2. Usual work-up refers to quenching the reaction with excess H_2O, extraction with CH_2Cl_2, drying the organic extracts over $MgSO_4$, and evaporation of the solvents under reduced pressure. For the sake of clarity the azetidin-2-one nomenclature will be used throughout this section.

Formation of the Dilithio Salts

General Procedure

The appropriate 2-azetidinone (approx. 0.5 g) was dissolved in THF (30 ml) at 0° and reacted with 2 equiv. of *n*-BuLi (1.9 *M* in hexane, Alfa Inorganics Inc.) The reaction mixture was stirred at 0° for 30–60 min. The appropriate electrophile was then added and the reaction mixture was stirred for an additional 5–10 min. The usual work-up gave the crude product which was purified by recrystallization or column chromatography over silica.

The azetidinones used in this study were prepared by cycloaddition of chlorosulfonyl isocyanate with the appropriate olefins (4) followed by reduction of the chlorosulfonyl group with Na_2SO_3 (5).

Reactions of 1,3-Dilithio-4-phenylazetidin-2-one (5a)

n-Butyl Bromide

To 4-phenylazetidin-2-one (400 mg) dissolved in 30 ml of THF at 0° was added 3.0 ml of *n*-BuLi solution. The reaction mixture was stirred for 1 h during which time the solution darkened considerably. *n*-Butyl bromide (400 mg) was added and the solution was allowed to stir for a further 20 min. The crude product obtained upon usual work-up was chromatographed (silica gel). Elution with ether yielded 330 mg (60%) of the *trans* isomer; n.m.r.: 0.8–2.1 (m, 9H), 2.95 (d of t, J = 2.0 and 7.0 Hz, 1H), 4.25 (d, J = 2.0 Hz, 1H), 7.0 (broad s, 1H), and 7.30 (s, 5H); i.r. peaks at 3270 and1753 cm^{-1}. Further elution with ether furnished 30 mg (6%) of the *cis* isomer; n.m.r.: 0.8–2.1 (m, 9H), 3.3 (m, 1H), 4.79 d(J = 5.5 Hz, 1H), 6.0 (broad s, 1H), and 7.2 (s, 5H). The N—H and C=O peaks of the *cis* isomer occurred at 3250 and 1745 cm^{-1} respectively.

Anal. Calcd. for $C_{13}H_{17}NO$ (the *trans* isomer): C, 76.83; H, 8.42. Found: C, 76.78; H, 8.40.

Methyl Iodide

To a solution of the dianion **5***a* prepared from 500 mg of **4***a* was added 0.26 ml (1 equiv.) of methyl iodide. Work-up, followed by careful chromatography gave 310 mg of a 4:1 *trans–cis* mixture of methylated products. Several recrystallizations from ether–pentane gave a

sample of the pure *trans* isomer, m.p. 95–96° (lit. (6) m.p. 99–100°). The n.m.r. of the *trans* isomer showed peaks at 1.30 (d, J = 7.5 Hz, 3H), 2.95 (d of q, J = 7.5 and 2.5 Hz, 1H), 4.21 (d, J = 2.5 Hz, 1H), 6.2 (s, 1H), and 7.26 (s, 5H).

Iodine

The solution of the dianion **5***a* prepared from 500 mg of **4***a* was added 864 mg of solid I_2. The reaction mixture was stirred at 0° for 30 min, then worked up. The crude product was purified by preparative t.l.c. The yield of *trans*-3-iodo-4-phenylazetidin-2-one was 150 mg (16%), m.p. 118–119°; n.m.r.: 4.67 (d, J = 2.1 Hz, 1H), 4.88 (d, J = 2.1 Hz, 1H), 6.9 (s, 1H), and 7.4 (s, 5H); i.r. 3420 and 1770 cm^{-1}.

Anal. Calcd. for C_9H_8INO: C, 39.58; H, 2.95; I, 46.47. Found: C, 39.83; H, 2.95; I, 46.29.

Acetone

Acetone (1 ml) was added to a solution of the dianion **5***a* prepared from 400 mg of **4***a*. Work-up gave 0.6 g of crude product whose n.m.r. indicated it to be mainly a mixture of the *trans* and *cis* adducts (5:1 ratio). Preparative t.l.c. yielded 380 mg 55% of crystalline material, m.p. 121–129°. The *trans* isomer showed the methyl groups as two singlets at 1.30 and 1.40, the C-3 H at 3.02 (d, J = 2.0 Hz), and C-4 H at 4.72 (J = 2.0 Hz). The corresponding peaks for the *cis* isomer occurred at 0.95 (s), 1.13 (s), 3.60 (d, J = 5.5 Hz), and 4.97 (d, J = 5.5 Hz).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 70.08, H, 7.34.

*Reactions of 1,3-Dilithio-4-vinylazetidin-2-one (**5***b*)

Benzophenone

Dianion **5***b* was generated at 0° from 500 mg of **4***b* and allowed to react with 910 mg of benzophenone. The crude product (1.48 g) was recrystallized from CH_2Cl_2–pentane. Yield, 1.24 g (88%), m.p. 186–190°. The n.m.r. spectrum was very complex but in general agreement with the expected product; i.r. peaks: 3600, 3420, 1750, 983, and 922 cm^{-1}.

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13. Found: C, 77.33; H, 6.16.

n-Butyl Bromide

n-Butyllithium (21 mmol) was added to a solution of 970 mg (10 mmol) of 4-vinylazetidin-2-one in 40 ml of THF. The reaction mixture was stirred for 1 h and 1.37 g (10 mmol) of *n*-butyl bromide was added. The crude reaction product was purified by chromatography on silica gel. Elution with 1:2 ethyl acetate – petroleum ether (35–60°) gave 1.19 g of *trans*-3-*n*-butyl-4-vinylazetidin-2-one; n.m.r.: 1.7–2.2 (m, 9H), 2.8–3.0 (m, 1H), 3.73 (d of d, J = 2.0 and 6.0 Hz, 1H) 5.6–6.4 (m, 3H), and 7.7 (s, 1H); i.r.: 3260, 3090, 1748, 1642, 985, and 920 cm^{-1}.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87. Found: C, 70.75; H, 9.79.

Isopropyl Bromide

To the dianion **5***b* generated from 500 mg of **4***b* was added 630 mg of isopropyl bromide. The reaction mixture was stirred for 15 min then worked up. The crude product was chromatographed (ether) to yield 315 mg (45%) of *trans*-3-isopropyl-4-vinylazetidin-2-one. The n.m.r. spectrum showed peaks at 0.98 (d, J = 6.0 Hz, 3H), 1.05 (d, J = 6.0 Hz, 3H), 1.65–2.35 (m, 1H), 2.62 (d of d, J = 2.2 and 7.5 Hz, 1H), 3.60 (d of d, J = 2.2 and 6.5 Hz, 1H), 5.0–6.3 (m, 3H), and 7.3–7.8 (s, 1H); i.r. peaks occurred at 3270, 3090, 1750, 1646, 985, and 920 cm^{-1}.

Anal. Calcd. for $C_8H_{13}NO$: C, 69.03; H, 9.42. Found: C, 69.49; H, 9.73.

Cyclohexanone

The crude product obtained from 500 mg of **4***b*, 12.0 mmol of *n*-BuLi and 490 mg of cyclohexanone was purified by preparative t.l.c. (ether–pentane 4:1). The colorless oil (480 mg, 55%) thus obtained had n.m.r. peaks at 1.0–2.0 (m, 10H) 1.7 (s, OH), 1.80 (d, J = 2.2 Hz, 1H), 4.02 (d of d, J = 2.2 and 6.0 Hz, 1H), 5.0–6.5 (m, 3H), and 6.8 (s, NH); i.r. peaks occurred at 3470, 3400, 1750, 978, and 930 cm^{-1}.

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.41; H, 8.63.

Reaction of 1,3-Dilithio-4-methyl-4-vinylazetidin-2-one with Benzophenone

Azetidin-2-one (**4***c*, 250 mg, 2.3 mmol) in 40 ml of THF at 0° was reacted with 5.0 mmol of *n*-BuLi for 0.5 h and then condensed with 420 mg of benzophenone. The crude product was recrystallized from ether–pentane to give 380 mg (57%) of adduct. Several further crystallizations gave one isomer as colorless crystals, m.p. 201–202°.

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53. Found: C, 77.84; H, 6.27.

Reactions of 1,3-Dilithio-4-ethylazetidin-2-one

n-Butyl Bromide

The crude product produced in the usual manner from 500 mg of 4-ethylazetidin-2-one and 685 mg of *n*-butyl bromide was chromatographed on silica gel. Elution with ether gave 506 mg (65%) of *trans*-3-*n*-butyl-4-ethylazetidin-2-one; n.m.r. 0.7–2.3 (m, 14 H), 2.6–3.0 (m, 1H), 3.50 (d of t, J = 1.8 and 6.0 Hz, 1H), and 7.7 (s, NH); i.r. peaks 3270 and 1755 cm^{-1}.

Benzophenone

The adduct was obtained in 65% yield. Recrystallization from ether–hexane gave colorless needles, m.p. 148–155°. The n.m.r. was in agreement with the expected structure.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81. Found: C, 76.93; H, 7.06.

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