

# Medium Ring Heterocycles: Transamidation Reactions of $\beta$ -Lactams

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Seven-, eight-, and nine-membered azalactams are easily prepared from azetidin-2-ones by transamidation *via* *N*-(halogenoalkyl) derivatives.

The problem of constructing medium-ring saturated heterocycles has long exercised synthetic chemists. We have been interested in the possibility of using the strain energy of the four-membered ring, and in particular of the azetidin-2-one ( $\beta$ -lactam) system, as the driving force for ring expansion to medium rings. In realisation of this objective we report a simple new sequence for transamidation of azetidin-2-ones under mild conditions<sup>1</sup> to give seven-, eight-, and nine-membered azalactams.

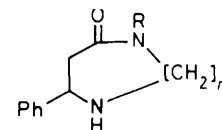
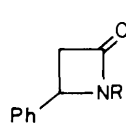
The substrate for most of these initial studies was 4-phenylazetidin-2-one (**1a**), easily accessible from styrene and *N*-chlorosulphonyl isocyanate.<sup>3</sup> Alkylation of (**1a**) with dihalogenoalkanes under phase-transfer conditions (powdered KOH, tetrahydrofuran, Bu<sub>4</sub>NHSO<sub>4</sub>; 20 °C)<sup>3</sup> led efficiently to the *N*-(halogenoalkyl) derivatives (**1b–e, g, h**)<sup>†</sup> (see Table 1). The *N*-(4-chlorobutyl) compound (**1f**)<sup>†</sup> was prepared by an alternative procedure [powdered KOH, dimethyl sulphoxide (DMSO); 20 °C].<sup>4</sup> Halides (**1b–g**), when treated with liquid ammonia in a sealed tube under the conditions outlined in Table 2 (entries 1–6), gave directly the corresponding seven-, eight-, and nine-membered ring-expanded azalactams in good yield: seven-membered (**2a**)<sup>†</sup> from (**1b**), eight-membered (**2b**)<sup>†</sup> from (**1c**) or (**1d**), and (**3**)<sup>††</sup> from (**1e**), and nine-membered (**2c**)<sup>†</sup> from (**1f**) or (**1g**). In an extension to other  $\beta$ -lactams, the *N*-(3-chloropropyl) derivatives (**4c**)<sup>†</sup> and (**4d**)<sup>†</sup>, prepared (Table 1) by the KOH–DMSO method from 4-pentyl- and 4-heptyl-azetidin-2-ones (**4a**)<sup>†</sup> and (**4b**)<sup>†§</sup> respectively, gave the corresponding azalactams (**5a**)<sup>†</sup> and (**5b**)<sup>†</sup> (Table 2, entries 7 and 8).

These reactions presumably involve intramolecular transamidation of *N*-(aminoalkyl) substitution products, and indeed in some cases these intermediates could be isolated. The *N*-(3-aminopropyl)azetidinone (**6a**)<sup>†</sup> was found along with the azalactam (**2b**) from reaction of either (**1c**) or (**1d**) (Table 2, entries 2 and 3; 3% and 17% respectively) and earlier

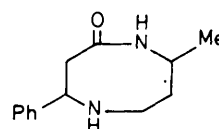
<sup>†</sup> New compounds gave spectra consistent with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.

<sup>††</sup> Azalactam (**3**) was isolated as a mixture of diastereoisomers from which the *trans*-isomer was crystallised and identified by *X*-ray crystallography. We thank Dr. M. J. Begley for this determination.

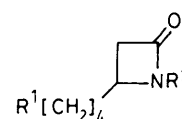
<sup>§</sup> Prepared by Grignard reagent addition to 4-phenylsulphonylazetidin-2-one (ref. 5).



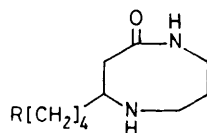
- (1) a; R = H  
 b; R = [CH<sub>2</sub>]<sub>2</sub>Br  
 c; R = [CH<sub>2</sub>]<sub>3</sub>Cl  
 d; R = [CH<sub>2</sub>]<sub>3</sub>Br  
 e; R = [CH<sub>2</sub>]<sub>2</sub>CHBrMe  
 f; R = [CH<sub>2</sub>]<sub>4</sub>Cl  
 g; R = [CH<sub>2</sub>]<sub>4</sub>Br  
 h; R = [CH<sub>2</sub>]<sub>5</sub>Br  
 i; R = CH<sub>2</sub>CH=CHMe
- (2) a; n = 2, R = H  
 b; n = 3, R = H  
 c; n = 4, R = H  
 d; n = 2, R = Et  
 e; n = 3, R = Et  
 f; n = 3, R = CH<sub>2</sub>CH=CH<sub>2</sub>  
 g; n = 4, R = CH<sub>2</sub>CH=CH<sub>2</sub>



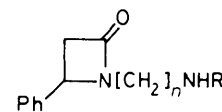
(3)



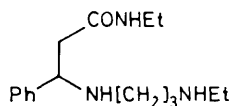
- (4) a; R<sup>1</sup> = Me, R<sup>2</sup> = H  
 b; R<sup>1</sup> = [CH<sub>2</sub>]<sub>2</sub>Me, R<sup>2</sup> = H  
 c; R<sup>1</sup> = Me, R<sup>2</sup> = [CH<sub>2</sub>]<sub>3</sub>Cl  
 d; R<sup>1</sup> = [CH<sub>2</sub>]<sub>2</sub>Me, R<sup>2</sup> = [CH<sub>2</sub>]<sub>3</sub>Cl



- (5) a; R = Me  
 b; R = [CH<sub>2</sub>]<sub>2</sub>Me



- (6) a; n = 3, R = H  
 b; n = 4, R = H  
 c; n = 5, R = H  
 d; n = 3, R = Et  
 e; n = 4, R = CH<sub>2</sub>CH=CH<sub>2</sub>  
 f; n = 3, R = CHMe<sub>2</sub>



(7)

Table 1. *N*-Alkylation of azetidinones with dihalogenoalkanes.

Azetidinone	Dihalogenoalkane	Dihalogenoalkane: azetidinone	Product (yield %)
(1a)	Br[CH <sub>2</sub> ] <sub>2</sub> Br	5:1	(1b) (48) <sup>a</sup>
"	Br[CH <sub>2</sub> ] <sub>3</sub> Cl	1:1	(1c) (94)
"	I[CH <sub>2</sub> ] <sub>3</sub> Br	3:1	(1d) (75)
"	Br[CH <sub>2</sub> ] <sub>3</sub> Br	3:1	(1d) (68)
"	Br[CH <sub>2</sub> ] <sub>2</sub> CHBrMe	1.5:1	(1e) (75)
"	Br[CH <sub>2</sub> ] <sub>4</sub> Cl	1:1	(1f) (70)
"	I[CH <sub>2</sub> ] <sub>4</sub> Br	3:1	(1g) (81)
"	Br[CH <sub>2</sub> ] <sub>5</sub> Br	5:1	(1h) (60)
(4a)	Br[CH <sub>2</sub> ] <sub>3</sub> Cl	3:1	(4c) (52)
(4b)	"	3:1	(4d) (60)

<sup>a</sup> Unchanged (**1a**) (50%) was recovered in this experiment.

**Table 2.** Ring expansion of *N*-(halogenoalkyl)azetidinones with amines.

Entry	Halide	Amine	Conditions	Product (yield %) <sup>a</sup>
1	(1b)	NH <sub>3</sub>	45 °C, 14 days	(2a) (70)
2	(1c)	"	20 °C, 6 days	(2b) (90)
3	(1d)	"	20 °C, 2 days	(2b) (80)
4	(1e)	"	60 °C, 5 days	(3) (71)
5	(1f)	"	60 °C, 7 days	(2c) (67)
6	(1g)	"	55 °C, 8 days	(2c) (65)
7	(4c)	"	50 °C, 3 days	(5a) (72)
8	(4d)	"	50 °C, 3 days	(5b) (85)
9	(1b)	EtNH <sub>2</sub>	45 °C, 7 days	(2d) (88)
10	(1c)	"	60 °C, 7 days	(2e) (46)
11	(1c)	CH <sub>2</sub> =CHCH <sub>2</sub> NH <sub>2</sub>	85 °C, 7 days	(2f) (55)

<sup>a</sup> Not optimised.

interception of the reaction of (1c) revealed increased proportions of (6a) as expected. The isolated amine (6a) underwent spontaneous transamidation to give (2b) either neat (approx. 40 days, 20 °C), or, more slowly, in CDCl<sub>3</sub> solution, but in both cases less rapidly than in liquid ammonia. When bromide (1g) was treated with liquid ammonia at 20 °C for 5 days (*cf.* Table 2, entry 5) the amine (6b)† was the major product (78%). Competition from elimination to give by-product (1i)† (18%) intervenes in the formation of (3) from secondary halide (1e) (Table 2, entry 4).

The more vigorous conditions necessary to produce (2c) (Table 2, entries 5 and 6), as compared with (2b) (Table 2, entries 2 and 3), presumably reflect the energetically less favourable seven-membered transition state required for transamidation in the former case when compared to the six-membered transition state for insertion of an aminopropyl unit to afford an eight-membered ring.<sup>6</sup> This is in accord with the isolation of amine (6c)† as the major product (60%), and no ten-membered azalactam, from the *N*-(5-bromopentyl)azetidinone (1h) after 7 days in liquid ammonia at 65 °C.

Alkyl primary amines can replace ammonia in this transamidation (Table 2, entries 9–11). Treatment of (1b) with ethylamine in a sealed tube gave the seven-membered *N*-ethyl azalactam (2d),† and similarly (1c) afforded *N*-alkyl azalactams (2e)† and (2f)† on reaction with ethyl- and allyl-amine, respectively. Substitution products (6d),† and (7)† from intermolecular transamidation, were isolated along with (2e) in proportions varying with the reaction conditions, and some acyclic *N*-allylamides were recovered with (2f). Nine-membered ring formation was again slower here, such that the *N*-(4-chlorobutyl)azetidinone (1f) was converted in boiling allylamine (53 °C, 3 days) into the amine (6e)† (58%) that underwent slow transamidation to give the azalactam (2g)† in toluene at reflux. Only the amine (6f)† was isolated (85%)

from reaction of (1c) with 2-aminopropane in a sealed tube (45 °C, 4 days), showing that the secondary alkyl group also hindered transamidation.

In exploration of the scope and application of this simple, new preparation of medium-ring lactams, the azalactam (2b) has been used by us in a synthesis of the spermine alkaloid homaline<sup>7</sup> and is potentially applicable to synthesis of the dihydroperiphylline group of macrocyclic spermidine alkaloids, whilst its homologue (2c) has been used in a synthesis of the celabenzine group.<sup>8</sup>

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