Medium Ring Heterocycles: Transamidation Reactions of β-Lactams

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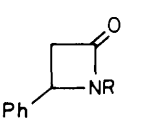
Seven-, eight-, and nine-membered azalactams are easily prepared from azetidin-2-ones by transamidation *via* *N*-(halogenoalkyl) derivatives.

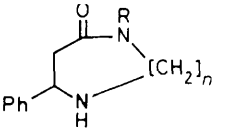
The problem of constructing medium-ring saturated heterocycles has long exercised synthetic chemists. We have been interested in the possibility of using the strain energy of the four-membered ring, and in particular of the azetidin-2-one (β-lactam) system, as the driving force for ring expansion to medium rings. In realisation of this objective we report a simple new sequence for transamidation of azetidin-2-ones under mild conditions[1] 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.[2] Alkylation of (**1a**) with dihalogenoalkanes under phase-transfer conditions (powdered KOH, tetrahydrofuran, Bu_4NHSO_4; 20 °C)[3] led efficiently to the *N*-(halogenoalkyl) derivatives (**1b—e, g, h**)† (see Table 1). The *N*-(4-chlorobutyl) compound (**1f**)† was prepared by an alternative procedure [powdered KOH, dimethyl sulphoxide (DMSO); 20 °C].[4] 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**)† from (**1b**), eight-membered (**2b**)† from (**1c**) or (**1d**), and (**3**)†‡ from (**1e**), and nine-membered (**2c**)† from (**1f**) or (**1g**). In an extension to other β-lactams, the *N*-(3-chloropropyl) derivatives (**4c**)† and (**4d**)†, prepared (Table 1) by the KOH–DMSO method from 4-pentyl- and 4-heptyl-azetidin-2-ones (**4a**)† and (**4b**),†§ respectively, gave the corresponding azalactams (**5a**)† and (**5b**)† (Table 2, entries 7 and 8).

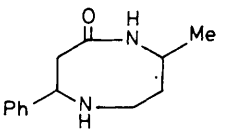
These reactions presumably involve intramolecular transamidation of *N*-(aminoalkyl) substitution products, and indeed in some cases these intermediates could be isolated. The *N*-(3-aminopropyl)azetidinone (**6a**)† was found along with the azalactam (**2b**) from reaction of either (**1c**) or (**1d**)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



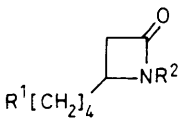
(**1**) **a**; R = H
b; R = $[CH_2]_2Br$
c; R = $[CH_2]_3Cl$
d; R = $[CH_2]_3Br$
e; R = $[CH_2]_2CHBrMe$
f; R = $[CH_2]_4Cl$
g; R = $[CH_2]_4Br$
h; R = $[CH_2]_5Br$
i; R = $CH_2CH{=}CHMe$



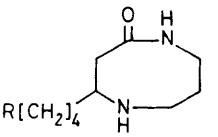
(**2**) **a**; *n* = 2, R = H
b; *n* = 3, R = H
c; *n* = 4, R = H
d; *n* = 2, R = Et
e; *n* = 3, R = Et
f; *n* = 3, R = $CH_2CH{=}CH_2$
g; *n* = 4, R = $CH_2CH{=}CH_2$



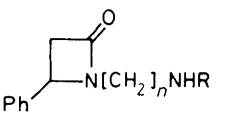
(**3**)



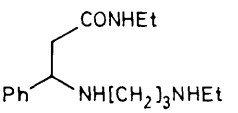
(**4**) **a**; R^1 = Me, R^2 = H
b; R^1 = $[CH_2]_2Me$, R^2 = H
c; R^1 = Me, R^2 = $[CH_2]_3Cl$
d; R^1 = $[CH_2]_2Me$, R^2 = $[CH_2]_3Cl$



(**5**) **a**; R = Me
b; R = $[CH_2]_2Me$



(**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 = $CH_2CH{=}CH_2$
f; *n* = 3, R = $CHMe_2$



(**7**)

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

‡ 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.

§ Prepared by Grignard reagent addition to 4-phenylsulphonyl-azetidin-2-one (ref. 5).

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

Azetidinone	Dihalogenoalkane	Dihalogenoalkane: azetidinone	Product (yield %)
(**1a**)	$Br[CH_2]_2Br$	5:1	(**1b**) (48)[a]
"	$Br[CH_2]_3Cl$	1:1	(**1c**) (94)
"	$I[CH_2]_3Br$	3:1	(**1d**) (75)
"	$Br[CH_2]_3Br$	3:1	(**1d**) (68)
"	$Br[CH_2]_2CHBrMe$	1.5:1	(**1e**) (75)
"	$Br[CH_2]_4Cl$	1:1	(**1f**) (70)
"	$I[CH_2]_4Br$	3:1	(**1g**) (81)
"	$Br[CH_2]_5Br$	5:1	(**1h**) (60)
(**4a**)	$Br[CH_2]_3Cl$	3:1	(**4c**) (52)
(**4b**)	"	3:1	(**4d**) (60)

[a] Unchanged (**1a**) (50%) was recovered in this experiment.

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

Entry	Halide	Amine	Conditions	Product (yield %)[a]
1	(**1b**)	NH_3	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**)	$EtNH_2$	45 °C, 7 days	(**2d**) (88)
10	(**1c**)	"	60 °C, 7 days	(**2e**) (46)
11	(**1c**)	$CH_2{=}CHCH_2NH_2$	85 °C, 7 days	(**2f**) (55)

[a] 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 $CDCl_3$ 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.[6] 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[7] 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.[8]

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