Studies in Heterocyclic Chemistry; Part XIV[1]. Preparation of Aziridine-2-carboxamides

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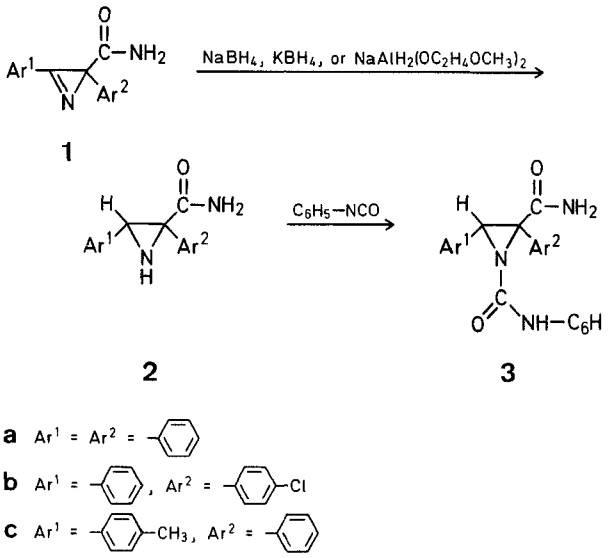
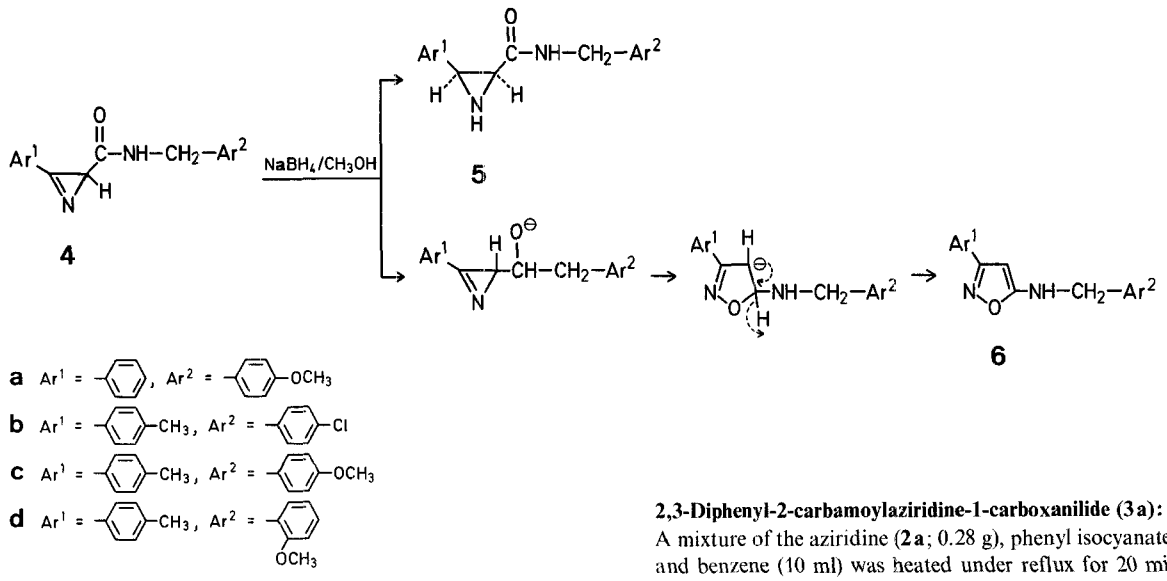
For other purposes, we needed a number of aziridine-2-carboxamides and attempted to reduce 2,3-diaryl-2*H*-azirine-2-carboxamides[2] and 3-aryl-2*H*-azirine-2-(N-benzylcarboxamides)[1] with lithium aluminium hydride, a reagent widely used for the reduction of the 2*H*-azirine C=N bond[3]. However, the reaction of 2,3-diphenyl-2*H*-azirine-2-carboxamide (**1**; $Ar^1=Ar^2=C_6H_5$) with this reagent gave the corresponding aziridine (**2**) in poor yield, and consequently we have studied the applicability of other complex metal hydrides for this reduction despite the discouraging report of Cram and Hatch[4]; these workers obtained 2-amino-3-methoxy-3-(2,4-dinitrophenyl)-propane or its positional isomer by the reaction of 3-methyl-2-(2,4-dinitrophenyl)-2*H*-azirine with sodium borohydride in methanol.

2,3-Diaryl-2*H*-azirine-2-carboxamides (**1a, b, c**) react readily with sodium borohydride or potassium borohydride in boiling methanol to give 2,3-diarylaziridine-2-carboxamides (**2a, b, c**) in up to 60% yield. Reduction of the 2*H*-azirine **1a** with sodium bis-[2-methoxyethoxy]-aluminum hydride[5] in cold benzene also proceeds smoothly to give the corresponding aziridine (**2a**) in good yield. It is known that this reducing agent reacts with carboxamide functions to afford the corresponding amine[5]; however, the amide group of the 2*H*-azirine **1a** was resistant to reduction even when two moles of reagent were employed. The I. R. and mass spectral data of the reduction products agree with structure **2**. The structure of compounds **2** was further confirmed by conversion into the urea derivatives **3** by reaction with phenyl isocyanate.



3-Aryl-2*H*-azirine-2-(N-benzylcarboxamides) (**4a–d**) can also be reduced to the corresponding *cis*-aziridines (**5**) in fair to good yield using sodium borohydride. The stereochemistry of products **5** was revealed by the N. M. R. spectra which displayed $J_{2H,3H}=7$–8 Hz[6].

From the reduction of **4c**, 5-(4-methoxybenzylamino)-3-(4-methylphenyl)-1,2-oxazole (**6c**) was isolated together with aziridine **5c**. This result can be explained by the assumption that hydride ion attacks the carbonyl group of **4c** and the resultant anion is rearranged and dehydrogenated to give **6c**.



a Ar^1 = C6H5, Ar^2 = C6H4-OCH3

b Ar^1 = C6H4-CH3, Ar^2 = C6H4-Cl

c Ar^1 = C6H4-CH3, Ar^2 = C6H4-OCH3

d Ar^1 = C6H4-CH3, Ar^2 = C6H4-OCH3

It is concluded that sodium borohydride is a suitable reagent for the selective reduction of the ring double bond in 2*H*-azirine-2-carboxamides.

Reduction of 2,3-Diphenyl-2*H*-azirine-2-carboxamide (1a) to 2,3-Diphenylaziridine-2-carboxamide (2a):

With Sodium Borohydride: A mixture of compound **1a** (1.18 g), sodium borohydride (0.14 g), and methanol (30 ml) was heated at reflux temperature for 30 min. The solvent was then evaporated and water was added to the residue. Compound **2a** crystallized from benzene/cyclohexane as needles; yield: 0.87 g (73%); m.p. 188–189°.

$C_{15}H_{14}N_2O$	calc.	C 75.60	H 5.92	N 11.76
	found	75.30	5.95	11.58

I.R. ($CHCl_3$): 3510 and 3390 (NH_2), 3250 (NH), and 1676 (C=O) cm^{-1}.

Mass spectrum: M^+ (*m/e* 238, 6%), $[M-CO-NH_2]^+$ (*m/e* 194, 17%), $[M-HCO-NH_2]^+$ (*m/e* 193, 100%).

With Potassium Borohydride: The reduction was carried out as described for sodium borohydride; yield: 71%.

With Sodium Bis-[2-methoxyethoxy]-aluminum Hydride: A mixture of sodium bis-[2-methoxyethoxy]-aluminum hydride (70% benzene solution; 3.8 g) and benzene (20 ml) was slowly added to a stirred and ice-cooled mixture of compound **1a** (2.4 g) and benzene (40 ml). The red solution was stirred for 15 min, acidified with 6 *N* hydrochloric acid, and poured into water. The precipitated product was isolated by filtration and recrystallized from benzene/cyclohexane; yield: 71%.

2-(4-Chlorophenyl)-3-phenylaziridine-2-carboxamide (2b):

A mixture of the 2*H*-azirine **1b** (1.35 g), sodium borohydride (0.20 g), and methanol (30 ml) was heated under reflux for 30 min. The solvent was evaporated, water was added to the residue, and the mixture was acidified with dilute hydrochloric acid. The aziridine was isolated and recrystallized from benzene/cyclohexane; yield: 67%; needles, m.p. 165°.

$C_{15}H_{13}ClN_2O$	calc.	C 66.05	H 4.81	N 10.27
	found	66.21	4.69	10.16

I.R. ($CHCl_3$): 3510 and 3390 (NH_2), 3260 (NH), 1678 (C=O) cm^{-1}.

3-(4-Methylphenyl)-2-phenylaziridine-2-carboxamide (2c):

This aziridine was obtained from **1c** similarly to above and crystallized from benzene/cyclohexane as needles; yield: 60%; m.p. 185–186°.

$C_{16}H_{16}N_2O$	calc.	C 76.16	H 6.39	N 11.10
	found	76.17	6.37	11.03

I.R. ($CHCl_3$): 3510 and 3390 (NH_2), 3250 (NH), 1676 (C=O) cm^{-1}.

2,3-Diphenyl-2-carbamoylaziridine-1-carboxanilide (3a):

A mixture of the aziridine (**2a**; 0.28 g), phenyl isocyanate (0.2 ml), and benzene (10 ml) was heated under reflux for 20 min. A precipitate (0.30 g, 71% yield) was obtained and crystallized from chloroform/petroleum ether as needles; m.p. 170°.

$C_{22}H_{19}N_3O_2$	calc.	C 73.93	H 5.36	N 11.76
	found	73.85	5.41	11.74

U.V. (ethanol): $\lambda_{max} = 237$ nm (log $\varepsilon = 4.43$).

3-Phenylaziridine-2-(N-4-methoxybenzylcarboxamide) (5a):

The 2*H*-azirine (**4c**; 0.78 g) and sodium borohydride (0.15 g) were heated under reflux in methanol (20 ml) for 2 hr. The solvent was evaporated and the residue was repeatedly extracted with ethyl acetate. The solvent was removed from the extracts and the aziridine crystallized from ligroin as needles; yield: 0.70 g (89%); m.p. 81–83°.

$C_{17}H_{18}N_2O_2$	calc.	C 72.32	H 6.43	N 9.92
	found	72.45	6.34	9.88

I.R. ($CHCl_3$): 3390 (NH), 3340 (NH), 1662 (C=O) cm^{-1}.

N.M.R. ($CDCl_3$): $\tau = 6.28$ ($J_{2,3} = 8$ Hz) (C_{2H}), 6.76 ($J_{2,3} = 8$ Hz) (C_{3H}).

3-(*p*-Tolyl)-aziridine-2-(N-4-chlorobenzylcarboxamide) (5b):

3-(*p*-Tolyl)-2*H*-azirine-2-(N-4-chlorobenzylcarboxamide) (**4b**) was prepared from 5-(4-chlorobenzylamino)-3-(*p*-tolyl)-1,2-oxazole (**6b**) as previously described[1] and was recrystallized from ethyl acetate/petroleum ether; m.p. 165–167° (correct analysis). The 2*H*-azirine (**4b**) was reduced with sodium borohydride as described above. Compound **5b** crystallized from ligroin as plates; yield: 51%; m.p. 125°.

$C_{17}H_{17}ClN_2O$	calc.	C 67.88	H 5.70	N 9.31
	found	67.63	5.68	9.25

I.R. ($CHCl_3$): 3370 (NH), 3320 (NH), 1662 (C=O) cm^{-1}.

N.M.R. ($CDCl_3$): $\tau = 6.28$ ($J_{2,3} = 7$ Hz) (C_{2H}), 6.76 ($J_{2,3} = 7$ Hz) (C_{3H}).

3-(*p*-Tolyl)-aziridine-2-(N-4-methoxybenzylcarboxamide) (5c):

3-(*p*-Tolyl)-2*H*-azirine-2-(N-4-methoxyphenylcarboxamide) (**4c**) was prepared from 5-(4-methoxybenzylamino)-3-(*p*-tolyl)-1,2-oxazole (**6c**) as previously described[1] and was recrystallized from ethyl acetate/petroleum ether; m.p. 188–189° (correct analysis). The 2*H*-azirine (**4c**) was reduced with sodium borohydride as described above and the reduction product was chromatographed on silica gel. Elution with petroleum ether/ether (2:1) gave a compound (0.14 g), which was recrystallized from ligroin and identified (m.p. and I.R.) as the 1,2-oxazole **6c**. Elution with ethyl acetate gave the aziridine **5c**, which was recrystallized from ligroin as needles; yield: 0.18 g (20%); m.p. 110–112°.

$C_{18}H_{20}N_2O_2$	calc.	C 72.95	H 6.80	N 9.45
	found	73.22	6.75	9.32

I.R. ($CHCl_3$): 3390 (NH), 3330 (NH), 1662 (C=O) cm^{-1}.

N.M.R. ($CDCl_3$): $\tau = 6.30$ (broad) (C_{2H}), 6.80 (broad) (C_{3H}).

3-(*p*-Tolyl)-aziridine-2-(N-2-methoxybenzylcarboxamide) (5d):
3-(*p*-Tolyl)-2*H*-azirine-2-(N-2-methoxybenzylcarboxamide) (**4d**) was prepared from 5-(2-methoxybenzylamino)-3-(*p*-tolyl)-1,2-oxazole (**6d**) as previously described[1] and was recrystallized from ethyl acetate/petroleum ether; m.p. 145–146° (correct elemental analysis). The 2*H*-azirine (**4d**) was reduced with sodium borohydride as described above and the product was recrystallized from petroleum ether as needles; yield: 79%; m.p. 101°. (Crystallization was difficult due to the tendency of **5d** to form a tar).

$C_{18}H_{20}N_2O_2$	calc.	C 72.95	H 6.80	N 9.45
	found	72.84	6.78	9.27

I.R. ($CHCl_3$): 3390 (NH), 3320 (NH), 1668 (C=O) cm^{-1}.

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