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ESTERS AND AMIDES FROM AZIRIDINE 2-CARBOXYLIC ACID SALTS

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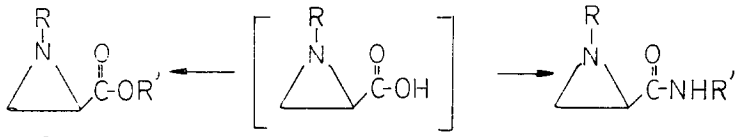
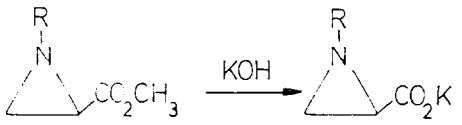
Summary : *Potassium salts of aziridine-2-carboxylic acid derivatives are efficiently converted into esters of amides by reactions with alkyl halides, alkyl dihalides or by acylation with trimethylacetyl chloride followed by aminolyses.*

Aziridine belongs to a class of alkylating compounds of importance in industry as well as in biology [1]. The activity of its derivatives is modulated by the ring substituents. In this work, we describe a easy method for the transformation of aziridine-carboxylic acids **1** into esters **2** or amides **3** in high yields :



2 **1** **3**

The carboxylic acids **1** are unstable but their potassium salts **4** [2] can be obtained by saponification of the readily available methyl esters **5** [3] with one equivalent of aqueous KOH. After water evaporation, the salts **4** can be stored for months at room temperature, under dry atmosphere.



5 **4**

4 a : R = $C(CH_3)_3$
4 b : R = $CH(CH_3)_2$
4 c : R = $CH(CH_3)C_6H_5$

The alkylation of salts **4** by alkyl halides **6** succeeds, without any N-alkylation, in refluxing acetonitrile in the presence of [18,6] crown ether [4]. The aziridines **7** are obtained in high yields, after purification by distillation or column chromatography (Table I) [5] :

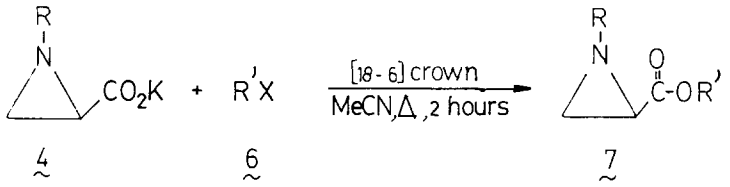


Table I : Synthesis of aziridines **7**

Compound	R	R'X	Yield (%)	B.P.: °C (Torr.)
7a	$(CH_3)_3C$	$BrCH_2CH=CH_2$	77	90 (0.8)
7b	"	$BrCH_2CH=CHCOOCH_3$	84	b
7c	"	$BrCH_2CH=CH-CH_2-CN$	88	b
7d	"	$BrCH_2CH=C(CH_3)(CH_2)_2CH=C(CH_3)_2$	84	b
7e	"	$BrCH_2C\equiv CH$	70	95 (0.8)
7f	"	$Cl-CH_2-C(=O)-CH_3$	84	b
7g	"	$Cl(CH_2)_2N(C_2H_5)_2$	84	b
7h	"	$Br-CH(OCH_3)COOCH_3$	58	b
7i	$(CH_3)_2CH$	$BrCH_2C\equiv CH$	74	93 (0.7)
7j	$C_6H_5(CH_3)CH$	$BrCH_2CH=CH_2$	84[a]	97 (0.01)

a) two isomers which were not separated.
b) purification by column chromatography on alumina.

Under these conditions, treatment of **4a** with α,β dihalides **8** affords the new bis-aziridine compounds **9** in good to fair yields (Table II)[5]:

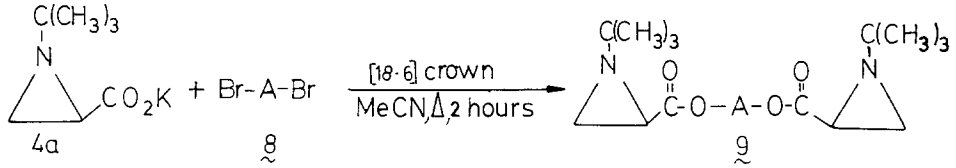
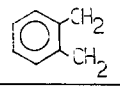


Table II : Synthesis of diaziridines **9**

Compound	A	Yield (%)
9a	$(CH_2)_3$	70
9b	$(CH_2)_4$	48
9c	$CH_2-CH=CH-CH_2$ (trans)	77
9d		52

The reaction of a suspension of **4a** in dichloromethane with trimethyl acetyl chloride leads to the mixed anhydride **10** which, without isolation[6], reacts with amines **11**, affording the carboxamido-aziridines **12** with good yields (Table III)[5,7]:

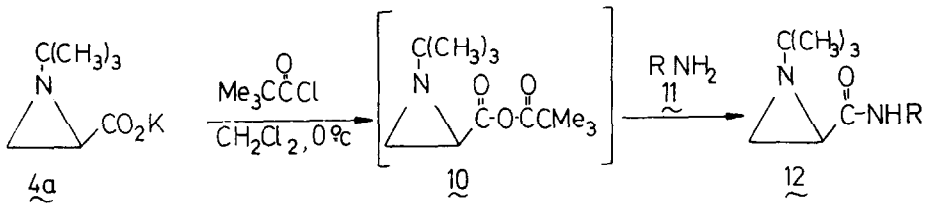
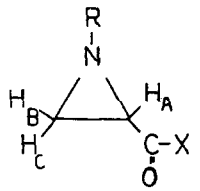


Table III : Synthesis of aziridines **12**

Compound	R	Yield (from **4a**)	m.p. or b.p.:°C (Torr.)
12a	H	84[8]	87
12b	$CH_2C_6H_5$	88	135 (0.1)
12c	$CH_2COOC_2H_5$	76[9]	67.5

Table IV summarizes the ^1H NMR characteristics of the ring protons of the aziridines **7**, **9** and **12** (TMS is used as internal standard):



Compound	δ_{H_A}	δ_{H_B}	δ_{H_C}	$^3J_{AB}$	$^3J_{AC}$	$^2J_{BC}$
7a	2.23	1.77	1.92	5.8	2.8	1.4
7b	2.25	1.80	1.93	6.3	3.0	1.4
7c	2.27	1.83	1.93	5.9	2.8	1.3
7d	2.26	1.80	1.96	6.2	2.9	1.4
7e	2.33	1.85	2.02	6.2	2.9	1.3
7f	2.32	1.86	1.99	6.0	2.9	1.4
7g	2.28	1.80	1.96	6.3	2.9	1.4
7h	2.19	1.75	1.83	6.0	2.8	1.5
7i	2.08	1.56	2.00	5.8	2.8	1.5
7j	2.34	1.80	2.10	6.5	3.1	1.1
7j'	2.23	1.61	2.14	6.4	3.1	1.0
9a	2.19	1.75	1.83	6.0	2.8	1.5
9b	2.20	1.75	1.90	6.2	2.8	1.5
9c	2.22	1.73	1.90	6.0	2.8	1.2
9d	2.20	1.73	1.92	6.4	3.1	1.2
12a	2.15	1.78	1.67	6.8	2.4	1.2
12b	2.27	1.78	1.60	6.3	2.6	1.6
12c	2.20	1.76	1.67	6.4	2.4	1.0

EXPERIMENTAL PART

2-carboalkoxy-aziridines 7 and 9 :

A mixture of 11 mmoles of **5**, 10 mmoles of **6** (or 5 mmoles of **8**) and 13mgrs (0.05 mmoles) of [18-6] crown ether in 15 mls of acetonitrile is refluxed during 2 hours. The solvent is then evaporated and 50 mls of water are added to the residue. Extraction by chloroform, followed by drying (Na_2SO_4) and evaporation afford crude **7** or **9** which are purified by distillation or column chromatography on alumina (see tables I, II).

2-carboxamido-aziridines 12 :

At 0°C, 4.8 grs (40 mmoles) of trimethyl-acetyl-chloride are added to a suspension of 7.6grs (42 mmoles) of **4a** in 80 mls of dichloromethane. After stirring during one hour at 0°C, 80 mmoles of amine are added (or a mixture of 40 mmoles of ethylglycinate hydrochloride and 80 mmoles of triethylamine in the case of **12c**). The mixture is let one hour at room temperature and washed with water. After drying and evaporation of the solvent, crude **12** are purified by distillation or column chromatography on alumina.

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