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OXIDATIVE RING-OPENING OF AZIRIDINE-1-CARBOXYLATES WITH SULPHOXIDES

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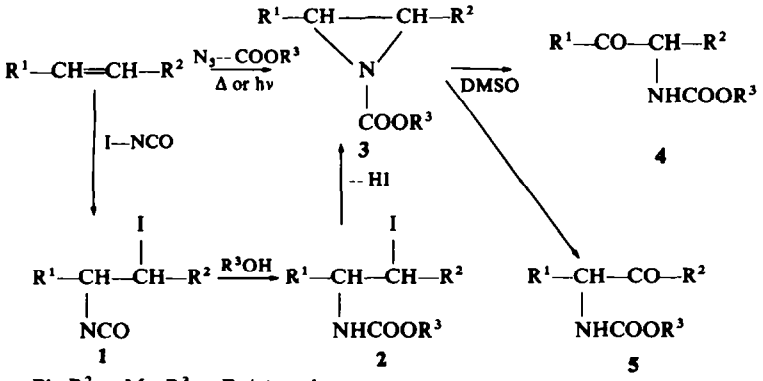
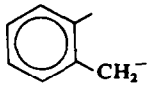
Abstract—The title reaction furnishes a practical preparation of α-carbalkoxyamino ketones from nitrene adducts of the corresponding olefins. The aziridines are alternatively accessible *via* addition of iodine isocyanate, alcoholysis and elimination of hydrogen iodide. DMSO-cleavage of *cis* and *trans* isomers of 1-carbethoxy-2-methyl-3-phenylaziridine preceeds regioselectively: the *cis* isomer reacts at 1,2-bond and 1,3-bond in a ratio of *ca* 1:1, whereas the *trans* isomer reacts at 1,3-bond almost exclusively. The 1,3-bond cleavage is predominant under acidic conditions for both isomers. Under neutral conditions, the cleavage proceeds *via* an S_N2 type transition state.

THE recorded reaction of 1-aroylaziridines with dimethyl sulphoxide (DMSO)[1] is of interest as a possible means of obtaining α-acylamino ketones, but the required aziridines are not easily accessible. The present paper deals with an extention of the



a: R^1 = Ph, R^2 = Me, R^3 = Et (*cis* and *trans*)
b: R^1, R^2 = —$(CH_2)_6$—, R^3 = Et
c: R^1 = Ph, R^2 = H, R^3 = Me
d: R^1, R^2 =  , R^3 = Et
e: R^1, R^2 = —$(CH_2)_4$—, R^3 = Et
f: R^1, R^2 = —$(CH_2CH_2CH{=})_2$, R^3 = Et

oxidative ring-opening to more readily available aziridine-1-carboxylates (**3**), which have been shown to give rise to α-carbalkoxyamino ketones (**4**, **5**) in preparative yields. Hitherto unknown regioselectivity of this reaction has been disclosed with respect to the *cis* and *trans* isomers of 1-carbethoxy-2-methyl-3-phenylaziridine (**3a**). The

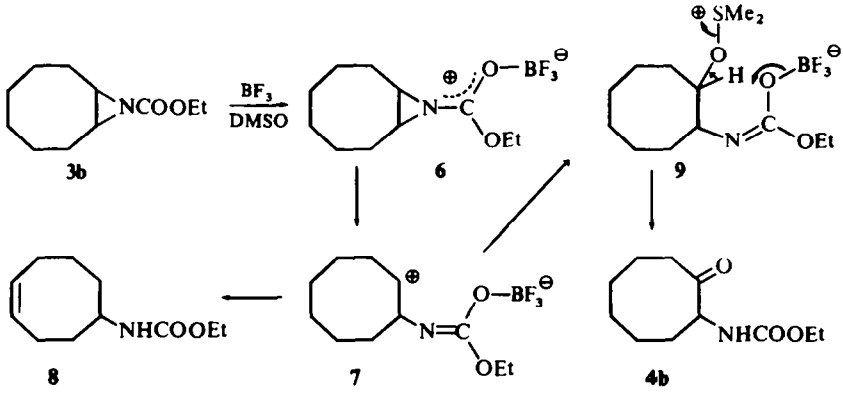
TABLE 1. PHYSICAL PROPERTIES OF NEW COMPOUNDS OBTAINED[a]

Compd	Yield (%)	b.p./mm. [m.p.] (solvent)	IR (cm^{-1})[b]	NMR (δ ppm)[c]
2b[d] (*trans*)	58	[78·5–78·9°] (EtOH)	3330, 1685, 1550,[e] 1375, 1270, 1245, 1090, 1038	5·4–5·0 (broad, 1H), 4·5–3·8 (m + q, 4H) 2·3–1·6 (m, 12H), 1·25 (t, 3H)
2c[f]	72	[101·6–102·2°] (MeOH)	3260, 1688, 1552,[e] 1280, 1267, 1043, 700	7·35 (s, 5H), 5·6–5·2 (broad, 1H), 5·0–δ4·7 (m, 1H), 3·70 (s, 3H), 3·52 (d, *J* 6 Hz, 2H)
3b[h]	56[i] 47[j]	103–110°/0·07	1720, 1470, 1370, 1294, 1278, 1227, 1100	4·05 (q, 2H), 2·4–0·9 (m + t (δ 1·25), 17H)
3c[k]	68[j]	90–93°/0·08	1725, 1445, 1320, 1305, 1280, 1230, 1200, 760, 700	7·18 (s, 5H), 3·63 (s, 3H), 3·37 (q, 1H), 2·55 (d, *J* 6 Hz, 1H), 2·13 (d, *J* 3·6 Hz, 1H)
3d[l]	45[j]	100–105°/0·05	1720, 1475, 1370, 1305, 1260, 1175, 1015, 795, 760, 725	7·5–7·0 (m, 4H), 3·9–2·7 (m + q, 6H), 0·85 (t, 3H)
3f[m]	65[i]	64°/0·06	1720, 1445, 1370, 1295, 1230, 1090, 1020	5·9–5·3 (m, 2H), 6·06 (q, 2H), 2·6–1·7 (m, 10H), 1·28 (t, 3H)
4a[n]	[o]	120°/0·04	3350, 1720, 1688, 1500–1530 (broad), 1450, 1225, 1095, 1065, 970, 700	8·1–7·9 (m, 2H), 7·6–7·4 (m, 3H), 5·90 (d, 1H), 5·25 (quintet, 1H), 4·06 (q, 2H), 1·38 (d, 3H), 1·22 (t, 3H)
5a[p]	[o]	[84·8–85·8°] (n-C_6H_{14}–AcOEt)	3340, 1710, 1495,[e] 1230, 1165, 1055, 700	7·28 (s, 5H), 6·2–5·9 (broad, 1H), 5·25 (d, 1H), 3·97 (q, 2H), 2·05 (s, 3H), 1·18 (t, 3H)
4b[q]	45	110–120°/0·05	3340, 1722, 1703, 1500–1530 (broad), 1370, 1330, 1250, 1195, 1086, 1042	5·8–5·5 (broad, 1H), 4·5–3·8 (m + q, 3H), 3·0–1·5 (m, 12H), 1·25 (t, 3H)
4c[r]	66	[97·4–97·8°] (AcOEt)	3340, 1726, 1698,[e] 1550, 1220, 1040, 690	8·1–7·9 (m, 2H), 7·7–7·4 (m, 3H), 6·0–δ5·6 (broad, 1H), 4·70 (d, *J* 5·4 Hz, 2H), 3·74 (s, 3H)
4f[s]	58	120–130°/0·15	3340, 1720, 1705, 1520, 1370, 1300, 1250, 1095, 1060, 1035, 740	6·0–5·3 (m, 3H), 4·6–3·7 (m + q, 3H), 3·0–1·2 (m, 8H), 1·20 (t, 3H)

[a] For the *trans* and *cis* isomers of **3a**, see Ref. 4.
[b] Neat unless otherwise stated.
[c] Determined in CCl_4 at 24°, 60 MHz unless otherwise stated.
[d] Found C, 40·8; H, 6·1; N, 4·4. $C_{11}H_{20}INO_2$ requires: C, 40·6; H, 6·2; N, 4·3%.
[e] Nujol.
[f] Found: C, 39·7; H, 3·9; N, 4·8. $C_{10}H_{12}INO_2$ requires: C, 39·4; H, 4·0; N, 4·6%.
[g] Determined in $CDCl_3$.
[h] Found: C, 67·0; H, 9·8; N, 7·1. $C_{11}H_{19}NO_2$ requires: C, 67·0; H, 9·7; N, 7·1%.
[i] Prepared by method (a).
[j] Prepared by method (b).
[k] Found: C, 67·6; H, 6·2; N, 7·7. $C_{10}H_{11}NO_2$ requires: C, 67·8; H, 6·3; N, 7·9%.
[l] Found: C, 71·1; H, 6·7; N, 6·7. $C_{12}H_{13}NO_2$ requires: C, 70·9; H, 6·5; N, 6·9%.
[m] Found: C, 67·4; H, 8·8; N, 7·0. $C_{11}H_{17}NO_2$ requires: C, 67·7; H, 8·8; N, 7·2%.
[n] Found: C, 65·4; H, 7·1; N, 6·1. $C_{12}H_{15}NO_3$ requires: C, 65·1; H, 6·8; N, 6·3%.
[o] The product ratio of **4a**/**5a** is given in Table 2.
[p] Found: C, 65·2; H, 6·8; N, 6·3. $C_{12}H_{15}NO_3$ requires: C, 65·1; H, 6·8; N, 6·3%.
[q] Found: C, 62·0; H, 9·0; N, 6·5. $C_{11}H_{19}NO_3$ requires: C, 61·9; H, 9·0; N, 6·6%.
[r] Found: C, 62·3; H, 5·6; N, 7·2. $C_{10}H_{11}NO_3$ requires: C, 62·2; H, 5·7; N, 7·3%.
[s] Found: C, 62·9; H, 8·4; N, 6·6. $C_{11}H_{17}NO_3$ requires: C, 62·5; H, 8·1; N, 6·6%.

mechanistic aspect of the reaction has been studied and it has been shown that the cleavage involves an S_N2 attack of DMSO on the ring carbon.*

α-*Carbalkoxyaminoketones.* Aziridine-1-carboxylates (**3**) have been prepared (a) by stereospecific addition of carbalkoxynitrene to olefins[3,4] or alternatively (b) by the addition of iodine isocyanate[5] to olefins, alcoholysis and the final ring closure.[4] DMSO-oxidation was carried out analogously on 1-aroylaziridines[1] by heating DMSO solutions of aziridines to afford good yields of the desired ketones (**4**, **5**). Under such neutral conditions, no transannular products were obtained in the oxidation of the aziridine (**3b**) derived from *cis*-cyclooctene. In contrast, however, heating in the presence of BF_3-etherate gave a transannular product **8** together with **4b**.



Compound **8** was identical with the authentic sample prepared by the addition of urethane to 1,5-cyclooctadiene. The reaction would probably proceed *via* **6**, **7** and/or **9**.† Physical properties and analyses of the compounds obtained in the present preparation are listed in Table 1.

Regioselectivity of the oxidation. Heating of the *trans* isomer of **3a** in DMSO afforded **4a** and a small amount of **5a** in a ratio given in Table 2, which contains product ratios obtained under various conditions and in the presence of other sulphoxides.

Remarkably, the *cis* isomer of **3a** reacted more sluggishly than the *trans* isomer and gave considerable amounts of the regioisomer **5a**. The *trans* isomer also afforded increased amounts of **5a** in the presence of bulky sulphoxides. This is explained by assuming an S_N2 type transition state (**10**) between *cis*-**3a** and **4a**. The nonbonded interaction between Me and Ph groups in the *cis* isomer inhibits the delocalization of developing plus charge on C_3,† which is incidentally more crowded than C_2. Such an effect is absent in the *trans* isomer of **3a**, which gives **4a** predominantly.

In the presence of less than a trace of acid, the exclusive product obtained in improved yields was **4a** for both isomers. This would be ascribed to S_N1 type bond cleavage affording the benzylic cation, which is then transformed to **4a**.§ These explan-

* Part of this work was presented in a communication form, see Ref. 2.

† Direct protonation of N-acylaziridine has been reported to result in carbonyl oxygen and not nitrogen protonation. See, Ref. 6.

‡ For this effect of a phenyl group in an S_N2 reaction, see Refs 7 and 8.

§ The acid-catalysed ring-opening of **3a** has been reported to involve the racemization of the configuration on C_3 corresponding to the S_N1 mechanism. See Ref 4.

ations are consistent with transannular results of the ring opening of **3b** as described above.

TABLE 2. OXIDATIVE CLEAVAGE OF **3a** WITH SULPHOXIDES

Substrate	Sulphoxide	Temp (°C)	Total yield[a] (%)	Product distribution[a] 4a (%)	5a (%)
trans-3a	DMSO[b,c]	120	82	93	7
	DMSO[b]	120	78	97	3
	DMSO[d]	120	96	100	0
	PhSOMe[b]	120	63	91	9
	i-PrSOMe[b]	120	62	87	13
cis-3a	DMSO[b,c]	140	56	40	60
	DMSO[b]	140	58	54	46
	DMSO[d]	120	95	100	0
	PhSOMe[b]	140	22	51	49
	i-PrSOMe[b]	140	*e*	*e*	*e*

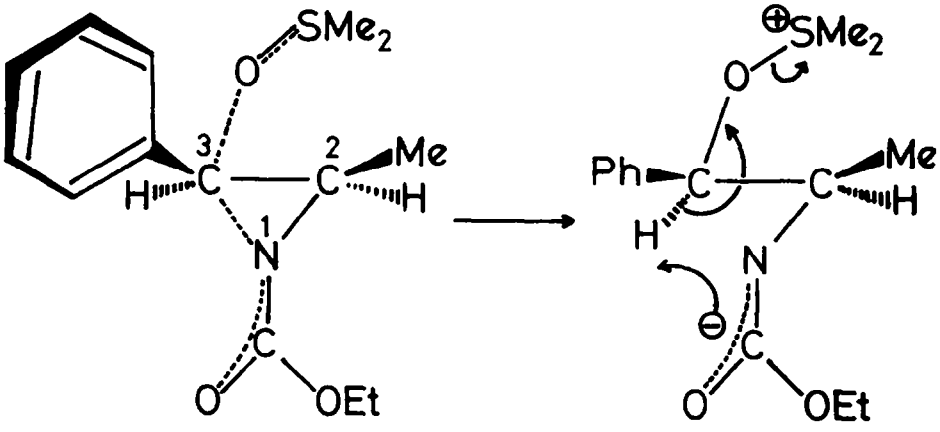
[a] Estimated by GC (High Vacuum Silicone Grease 30% on Celite 545, 200° or Versamid 900 10% on Celite 545, 184°) using 4,5-decamethylene-1,3-dioxolen-2-one as an internal standard. Unless otherwise stated, they were determined directly on crude mixtures. The reaction was continued for 24 hr in each case.

[b] The reaction was performed in a vessel previously washed with aq sodium hydroxide and water.

[c] The total yield and product distribution were determined after single distillation.

[d] The reaction was performed in a vessel previously washed with sulphuric acid and water.

[e] No oxidation products were detected by GC.



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EXPERIMENTAL

All m.ps are uncorrected. NMR spectra were obtained on a JEOL C-60-H spectrometer at 60 MHz, 24° and mass spectra on a Hitachi RMS-4 spectrometer. Gas chromatographic analyses (GC) were performed on High Vacuum Silicone Grease 30% on Celite 545 (2 m) or Verasmid 900 10% on Celite 545 (2 m). Sulphoxides used were heated under reflux over calcium hydride, distilled and stored over molecular sieves. The physical properties and analyses of new compds are collected in Table 1.

Ethyl trans-2-*iodocyclooctane*-1-*carbamate* (**2b**). Iodine (19 g, 75 mmoles) was added at 0° in one portion to a mixture of cyclooctene (8·25 g, 75 mmoles), silver cyanate (15 g, 100 mmoles) and dry ether (110 ml). Stirring was continued for 7 hr at 0°, then for 4 hr at room temp. After filtration of the AgI, EtOH (100 ml) containing a small amount of NaOEt (100 mg) was added to the filtrate, which was allowed to stand in the dark for 3 days. The solvent was evaporated *in vacuo* and the residue was poured onto ice–water containing Na_2SO_3 (5 g), extracted with ether and dried (Na_2SO_4). Evaporation of the solvent under vacuum gave a crude solid. Recrystallization afforded **2b** (14·0 g).

9-*Carbethoxy*-9-*azabicyclo*[6.1.0]*nonane* (**3b**). A mixture of ethyl azidoformate (5·0 g) and cyclooctene (70 ml) in a quartz tube was irradiated with a 200 W high pressure Hg arc until N_2 evolution had ceased (*ca* 40 hr). Distillation *in vacuo* gave **3b** as a colourless oil (4·8 g).

The aziridine (**3b**) was also obtained by dehydriodination of **2b**.

Methyl 2-*iodo*-1-*phenylethane*-1-*carbamate* (**2c**) was prepared from styrene (7·8 g, 75 mmoles) by the method similar to the one reported.[5]

1-*Carbomethoxy*-2-*phenylaziridine* (**3c**). A soln of **2c** (6·08 g, 20 mmoles) in dry benzene (60 ml) was added dropwise to NaH (2·2 g) suspended in dry benzene (30 ml) during 1 hr under N_2 at 55–60°. After an additional stirring for 3 hr at 55–60°, insoluble materials were filtered off, washed with dry ether and the combined filtrates were carefully concentrated below 40°. Immediate distillation yielded **3c** as a colourless oil (2·4 g).

N-*Carbethoxy*-1,2-*iminoindene* (**3d**) was prepared by dehydriodination of ethyl *trans*-2-iodoindan-1-carbamate[5] (2·2 g) as described above. The aziridine (0·61 g), thermally very unstable, was contaminated by a small amount of an isomerized product. The analytical sample was obtained by chromatography on alumina (elution with n-hexane-benzene 1:3).

9-*Carbethoxy*-9-*azabicyclo*[6.1.0]*non*-4-*ene* (**3f**). A mixture of 1,5-cyclooctadiene (70 ml) and ethyl azidoformate (5·0 g) was irradiated for 40 hr as described. Distillation yielded aziridine (**3f**).

Oxidation of aziridines with sulphoxides

General procedure. A soln of aziridine in dry sulphoxide was heated at 120° under N_2 for 24 hr. After cooling, the mixture was poured into NaCl aq, extracted 4 times with ether and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* and careful distillation afforded the corresponding α-carbalkoxy aminokentone.

Oxidation of 1-*carbethoxy*-2-*methyl*-3-*phenylaziridine* (**3a**). The *trans*-isomer[4] of **3a** (1·64 g, 80 mmoles) was oxidized with DMSO. Distillation and subsequent preparative GC gave **4a** and ethyl **5a**. The former was identical with the authentic sample described below.

The *cis*-isomer[4] of **3a** (0·25 g, 2 mmoles) was oxidized with DMSO as described. Distillation gave a mixture of **4a** and **5a**.

The product distributions were determined by GC as shown in Table 2, which also summarizes the results of oxidation with sulphoxide under various conditions.

Ethyl cyclooctane-2-*one*-1-*carbamate* (**4b**; 0·58 g) was obtained by DMSO-oxidation of **3b** (1·18 g, 6 mmoles).

Methyl N-*phenacylcarbamate* (**4c**). Aziridine (**3c**; 0·50 g, 3 mmoles) was oxidized with DMSO. Distillation and recrystallization gave **4c** (0·36 g) as colourless plates. GC analysis of the crude product showed no contamination by other products.

Ethyl cyclohexan-2-*one*-1-*carbamate* (**4e**). Aziridine[9] (**3e**; 1·71 g, 10 mmoles) was oxidized with DMSO to afford **4e** as a colourless oil (1·21 g, 65%)—the spectral data are identical with an authentic sample.[10]

Ethyl cyclooct-5-*en*-2-*one*-1-*carbamate* (**4f**). Aziridine (**3f**; 1·06 g, 53 mmoles) was oxidized with DMSO. Distillation and following chromatography on Silicagel afforded the corresponding **4f** (0·66 g).

Isomerization of N-*carbethoxy*-1,2-*iminoindene* (**3d**) *in* DMSO. A soln of **3d** (0·40 g, 2 mmoles) in dry DMSO (5 ml) was heated at 120° under N_2 for 24 hr. After usual work-up, chromatographic separation on Silicagel afforded **11** (0·19 g, 48%), m.p. 149–150° (acetone); IR (Nujol): 3330, 1702, 1550, 1308, 1240, 1055, 832, 747, 714 cm^{-1}; NMR ($CDCl_3$): δ 7·5–6·7 (m, 5H), 6·50 (s, 1H), 4·24 (q, 2H), 3·63 (s, 2H), 1·32 (t, 3H). MS (m/e): 203 (M^+). (Found: C, 71·0; H, 6·3; N, 6·9. $C_{12}H_{13}NO_2$ requires: C, 70·9; H, 6·5; N, 6·9%).

N-*Carbethoxy*-α-*aminopropiophenone* (**4a**). A mixture of sodium dichromate dihydrate (0·6 g, 2 mmoles), conc H_2SO_4 (1·5 ml) and water (15 ml) was added dropwise at 20° to a soln of N-carbethoxypseudonorephedrine (1·12 g, 5 mmoles)[4] in ether (30 ml). After usual work-up, distillation *in vacuo* gave **4a** as a colourless oil (1·0 g, 89%). The spectral data are given in Table 1.

BF_3-*catalyzed reaction of* **3b** *in* DMSO. A soln of BF_3-etherate (0·1 ml) in DMSO (5 ml) was added under N_2 to **3b** (0·30 g, 1·5 mmoles) and heated at 120° for 8 hr. After usual work-up, distillation and preparative

TLC, **8** (0·14 g, 47%) and the oxidation product **4b** (0·07 g, 22%) were obtained. The retention times on GC and the IR spectrum of each compd are identical with those of an authentic sample.

Ethyl cyclooct-4-ene-1-carbamate (**8**) was prepared from 1,5-cyclooctadiene according to the reported method.[11] A soln of 1,5-cyclooctadiene (2·70 g, 25 mmoles) in dry xylene (3 ml) was added dropwise under N_2 to a mixture of urethane (23 g, 25 mmoles), BF_3-etherate (2 ml) and xylene (8 ml) during 2·5 hr at 80–90°. The mixture was heated at 100° for 22 hr. After usual work-up, chromatography on alumina and distillation gave **8** as an oil (0·70 g, 17%), b.p. 100–110°/0·06 mm; IR (neat): 3340, 1690, 1525, 1225, 1096, 1045 cm^{-1}; NMR (CCl_4): δ 5·8–5·5 (m, 2H), 5·0–4·4 (broad, 1H), 4·04 (q, 2H), 3·9–3·3 (m, 1H), 2·5–1·2 (m, 8H), 1·24 (t, 3H). (Found: C, 67·1; H, 10·0; N, 6·9. $C_{11}H_{19}NO_2$ requires: C, 67·0; H, 9·7; N, 7·1%).

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