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NUCLEOPHILIC CLEAVAGE OF 2,2-DIMETHYLAZIRIDINES: COMPETITION BETWEEN S_N2 AND POSTULATED "SET" MECHANISM.[1]

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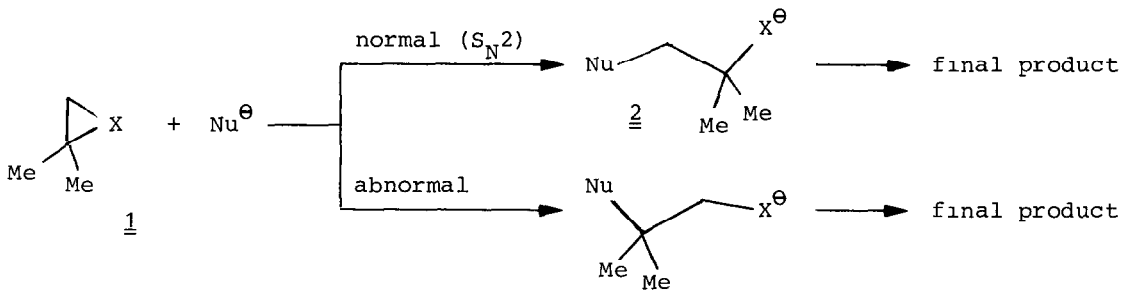
Abstract: Regioselectivity of nucleophilic attack on 2,2-dimethylaziridines depends on the degree of leaving group activation in highly activated aziridines it occurs at the methylene carbon and in less activated at the tertiary carbon This latter abnormal ring opening is explained by an SET mechanism

Nucleophilic ring opening of activated aziridines proceeds via an S_N2-like mechanism[2]. Many results (e.g. ref.[1] and preceding papers) are consistent with this, at least in the absence of acid catalysis which may favour S_N1 behaviour in suitable cases. However, the known behaviour of 1 does not fit into this scheme: see reactions 1-3 in Table I[3]. The activation of the aziridine is strongest (best leaving groups $X^{\ominus}$) in reactions 1 and 2 which yield the "normal" products. Surprisingly, the weakest activated aziridine yields the "abnormal" product (reaction 3). It is difficult to understand why precisely this reaction should prefer an S_N1-like mechanism, especially since the reaction conditions would certainly not have favoured this. Thus, we considered the possibility of a radical intermediate in reaction 3 and began a study of 1.



X = nitrogen function

$Nu^{\ominus}$ = nucleophile

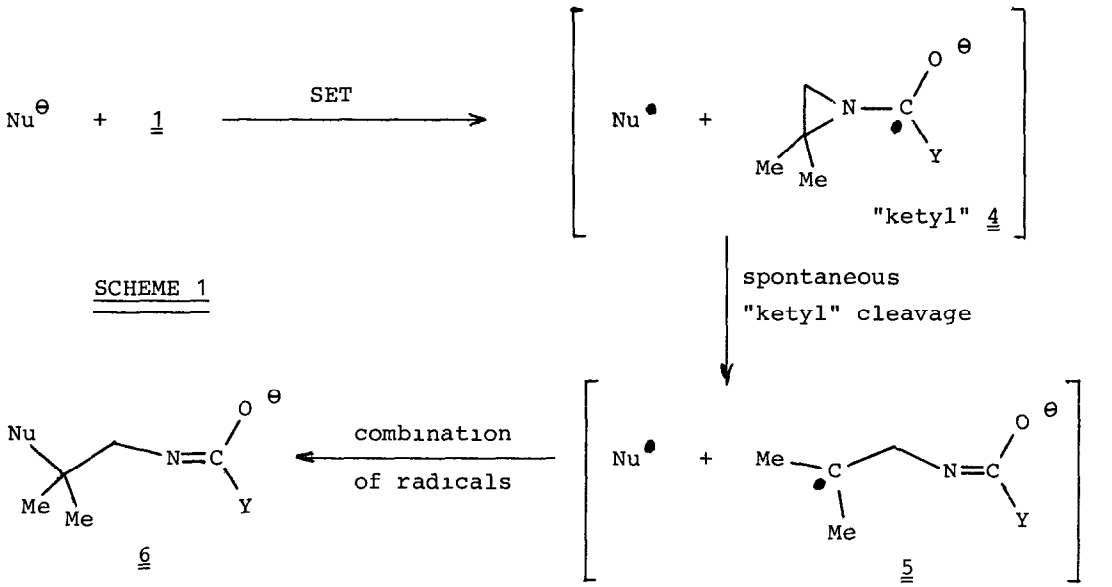
As shown in Table I, exclusively "abnormal" reaction in examples with low aziridine activation (acyl, dinitrophenyl) was found and exclusively (except reactions 17-18) "normal" reaction was found in those with strongly activated (e.g. sulfonyl) aziridines. On the basis of this we propose a single electron transfer mechanism depicted in SCHEME 1 with an acyl aziridine. The first

Table I. Type of product obtained from 1 at room temperature (except No. 1-3).

No.	X	nucleophile	product/yield/ e = exclusive/m.p.
1	$\overset{\oplus}{N}HCH_2CH_2Ph$	$LiCH(CO_2Et)_2$ (chelated ion pair)	normal/52%/e [4]
2	NTs	$Ph_2C^{\ominus}{=}CN$	normal/70% [5]
3	NCO_2Et	"	abnormal/40% [5]
4	NCOPh	$p\text{-}Ph\text{-}C_6H_4\text{-}CH^{\ominus}{=}CN$	abnormal[6]/74%/e/170°C
5	"	$EtPhC^{\ominus}{=}CN$	abnormal[6]/42%/e/141°C
6	"	$Ph\text{-}C(^{\ominus}CN)(CO_2Et)$	abnormal[6]/60%/e/135°C
7	NCONHPh	"	abnormal[7]/63%/e/164°C
8	NTs	$^{\ominus}CH(CO_2Et)_2$	normal[8]/62%/e/110°C
9	"	$Me\text{-}C(^{\ominus}CN)(CO_2Et)$	normal[8]/not yet dtd./e ?/154°C
10	NCOPh	"	abnormal[7]/68%/e/144°C
11	NTs	$Fluorenyl^{\ominus}$	normal[9]/42%/e/163°C
12	NCOPh	"	abnormal[6]/80%/e/121°C
13	NTs	Piperidine	normal[9]/92%/e/68°C
14	$NC_6H_3(NO_2)_2(2,4)$	"	abnormal[6]/81%/e/129°C
15	NCOPh	"	abnormal[6]/90%/e/76°C
16	$NCOC_6H_4NO_2(4)$	Morpholine	abnormal[6]/77%/e/122°C
17	NSO_2Ph	PhNHMe	54% abnormal[6]/91°C, 31% normal[9]/74-75°C
18	NTs	$PhNH_2$	abnormal[6]/73%/e/129°C

step is probably the rate determining; it may include the intermediate formation of a molecular complex. The radical anion formed in this step is termed "ketyl" because the carbonyl function of an acyl aziridine resembles rather a ketone than a carboxamide, and because thus it can be easily distinguished from the "anionic" radical 5 that is formed in the next step.

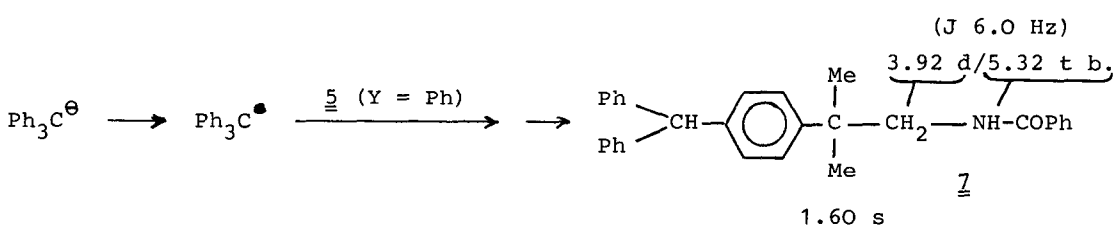
The "normal" reaction of 1 resembles a nucleophilic substitution in neopentyl position and will therefore be slow. With low activation, it will be extremely slow, enabling SET to occur. Only high activation accelerates the "normal" reaction sufficiently to make it faster than SET. Thus, the "abnormal" reaction with the nucleophiles of Table I was rather slow. the yield in reaction 12 was 80 % after 8 days and only 42 % after 3 days; reaction 13 was completed after 16 hours, reaction 15 after 15 days. As expected, reaction 16 proceeded faster than reaction 15 because of the rate determining SET step; electron attachment as well as complex formation will be facilitated by the additional nitro group in reaction 16.



SCHEME 1

A radical chain mechanism ($S_{RN}1$, Kornblum reaction[10]), which we had considered first, was ruled out because of the slow "abnormal"reaction.An even more important argument against the chain mechanism is provided by reactions 14 and 15 because in these cases the anion 6 is not able to form the necessary intermediate which carries an excess electron. - In reactions 17 and 18 the nucleophile is a bad one (slowing down the "normal" reaction) but an efficient electron donor (accelerating the SET step). Thus the preference of the sulfonyl aziridines for the "normal" reaction is drastically diminished.

Stirring 1 (X = NCOPh) with sodium dispersion in THF provided a mixture of 25 % $Me_2CHCH_2NHCOPh$ [m.p. 56°C (lit.[11] liquid), PMR: Me_2 0.93 d (J 6 Hz), CH 1.88 mc, CH_2 3.23 t (J 6.5 Hz), NH 7.03 t brd. (J ≈ 6.5 Hz)] and 20 % $Me_2C{=}CHNHCOPh$ [oil, PMR: Me/Me 1.73 s/1.76 s, CH 6.73 d (J 10.2 Hz), NH hidden]. This may be rationalized by successive formation of "ketyl" 4 and "anionic radical" 5 followed by disproportionation of 5. - Reaction of anthracene radical anion with 1 (X = NCOPh) proceeded fast,yielding as major product 3+H⊕[Nu = 9,10-dihydroanthracenyl-9, X = NCOPh, m.p. 145°C, PMR: 10-CH_2 3.77 d/4.16 (J 18.8 Hz), 9-CH 3.82 s, CH_2 3.37 d (J 6.0 Hz), NH 5.92 t brd. (J ≈ 6 Hz)]. - Reaction of trityl anion with 1 (X = NCOPh) yielded mainly 7 (m.p. 230°C) as expected due to the known behaviour[12] of the trityl radical:



References and Notes

[1] Reactions with Azirıdınes, Part 27. - Part 26.: H. Stamm and V. Gaılıus, Chem. Ber. 114, 3599 (1981).

[2] G. E. Ham, J. Org. Chem. 29, 3052 (1964).

[3] Important PMR data (aryl protons and nucleophile protons omitted) of products and melting points are given throughout this paper. All products of this work were not previously described and gave satisfactory CHN analyses as well as spectral data (IR- PMR) confirming their structures. An "abnormal" structure is revealed (among other data) by a PMR CH_2 doublet (vicinal coupling with NH) for the amido-tert-butyl substructure.

[4] H. Stamm, Arch. Pharm. (Weinheim) 299, 965 (1966).

[5] W. Klotzer, Monatsh. Chem. 101, 1841 (1970).

[6] Protonated 3 is the final product. PMR: No. 4: Me/Me 1.10 s/1.19 s, CH_2 3.50 d (J 6.2 Hz), CH 3.75 s, NH 6.10 t brd. (J ≈ 6 Hz).- No. 5: Me/Me 1.10 s/1.20 s, CH_2 3.53 d (J 6.2 Hz), NH 6.07 t brd. (J 6.2 Hz).- No. 6: Me/Me 1.27 s/1.34 s, CH_2 3.64 d (J 6.5 Hz), NH 6.70 t brd. (J 6.5 Hz).- No. 12: Me_2 1.30 s, CH_2 3.17 d (J 6.2 Hz), NH 5.53 t brd. (J 6.2 Hz).- No. 14. Me_2 1.17 s, CH_2 3.24 d (J 4.2 Hz), NH 9.46 s very brd..- No. 15: Me_2 1.07 s, CH_2 3.34 d (J 4.4 Hz), NH 7.24 s very brd..- No. 16: Me_2 1.15 s, CH_2 3.41 d (J 4.4 Hz), NH 7.22 t brd. (J ≈ 4 Hz).- No. 17 abnormal: Me_2 0.98 s, CH_2 2.87 d (J 3.3 Hz), NH 5.40 s very brd..- No. 18: (Ph)NH 3.32 s very brd., Me_2 1.23 s, CH_2 3.01 d (J 5.8 Hz), NH 5.09 t brd. (J ≈ 6 Hz).

[7] The corresponding pyrrolidone (3 - $EtO^{\ominus}$) is the final product, in no. 10 the nitrogen is debenzoylated. PMR: No. 7: Me/Me 0.80 s/1.48 s, CH_2 3.69 d/3.87 d (J 11.4 Hz).- No. 10: Me/Me/Me 1.13 s/1.35 s/1.45 s, CH_2 3.20 s, NH 7.76 s brd..

[8] The corresponding N-Ts pyrrolidone (2 - $EtO^{\ominus}$) is the final product. PMR: No. 8: Me/Me 1.66 s/1.77 s, ring-CH_2 1.97-2.63 m, ring-CH 3.51 t (J 9.7 Hz).- No. 9: Me/Me/Me 1.56 s/1.76 s/1.83 s, CH_2 1.98 d/2.57 d (J 13.5 Hz).

[9] Protonated 2 is the final product. PMR: No. 11: CH 3.95 t (J 8.0 Hz), CH_2 2.32 d (J 8.0 Hz), Me_2 1.20 s, NH 5.19 s brd..- No. 13: CH_2 2.23 s, Me_2 1.11 s, NH 5.53 s very brd..- No. 17 "normal": CH_2 3.39 s, Me_2 1.22 s, NH 5.19 s brd..

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