PEROXIDATION OF AZIRINES. A SEARCH FOR OXAZABICYCLOBUTANES.[1]

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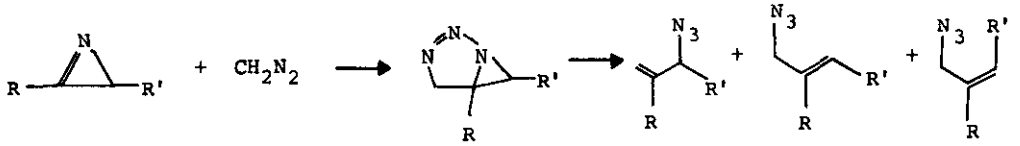
Abstract: Nucleophilic as well as electrophilic epoxidation of azirines leads to N-acylimines or their derivatives, possibly by way of an oxazabicyclobutane.

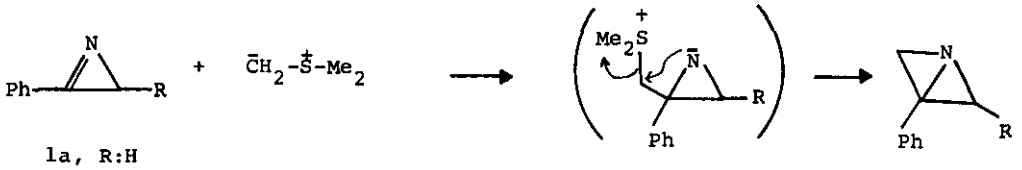
INTRODUCTION

In the last few years the chemistry of azirines 1 has received considerable attention, especially since these compounds can serve as synthons for a variety of other heterocyclic molecules.[2] These strained small ring heterocycles (1) can behave as both electrophiles or nucleophiles with appropriate reagents. Among the interesting reactions that azirines 1 undergo is the formation of the strained azabicyclobutane compounds 4. Early attempts to prepare azabicyclobutanes 4 by reaction of azirines 1 with diazo compounds[3] generated allyl azides, presumably via cycloaddition to an intermediate 2. However, treatment of 1 with



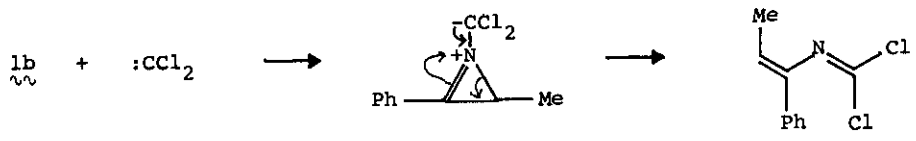
1 2

trimethylsulfonium ylid leads, most likely via 3, to isolation of azabicyclobutanes 4.[4,5]



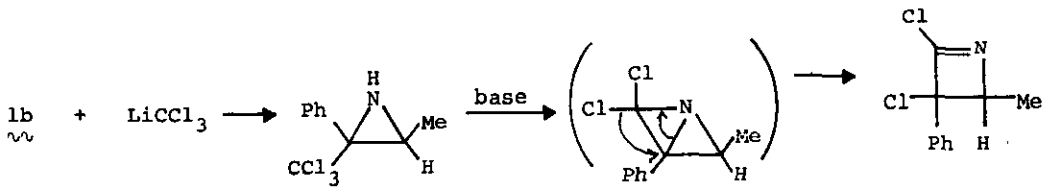
1a, R:H
1b, R:Me 3 4

On the other hand, dichlorocarbene (generated by decomposition of phenylmercuric trichloromethane) reacts with 1b, presumably via intermediate 5 to produce *open* chain dichloroimines 6.[5]



5 6

The formation of azetine 9 has been postulated to proceed via the isolable adduct 7 and the nonisolable intermediate azabicyclobutane 8.[5]

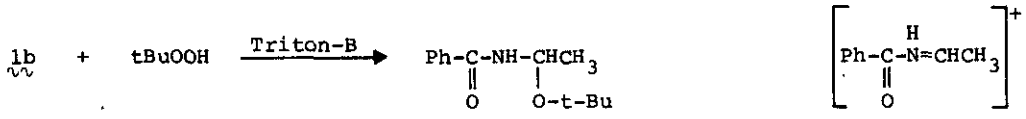


7 8 9

Heterocyclic analogs of 4 have, so far, been elusive. Attempts to epoxidize azirine 1 with m-chloroperbenzoic acid in methylene chloride to an oxazabicyclobutane were unsuccessful and led to an inseparable mixture of products.[6]

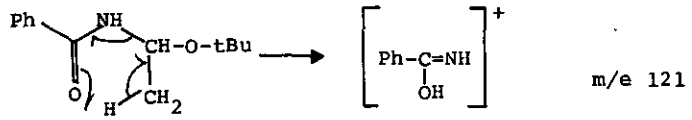
RESULTS AND DISCUSSION

We felt that nucleophilic addition of a peroxide anion to 1 (in analogy to 1 → 3 → 4 and 1 → 7 → 8) may have a better chance for success. Indeed, t-butyl hydroperoxide reacts with 1b in the presence of Triton-B to produce a neutral compound (21%) identified as N-(1-t-butoxy ethyl)benzamide 10 and 2,5-dimethyl-3,6-diphenylpyrazine (9%). The latter probably arose from a hydrolysis-dimerization of the azirine 1b.



10 i

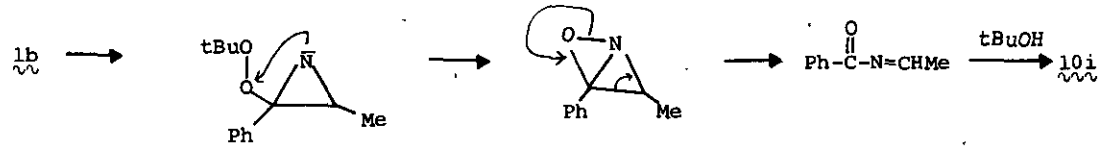
The structure of 10 was obvious from its elemental analysis, ir at 3350 (NH), and 1650 cm^{-1} (C=O-N), nmr and mass spectra. The H-nmr spectrum showed a broad one proton singlet for the NH at δ7, which disappeared on D_2O addition; a one proton multiplet at 5.8-6.2 and a CH_3 doublet, J=6 Hz at 1.48, in addition to the aromatic and t-butyl signals. Though no M^+ peak was noticed in the mass spectrum, a major peak (40%) resulting from fragmentation to i (m/e 148) was present, as well as a 121 peak (1%) resulting from a McLafferty rearrangement of 10; the base peak was at m/e 105 (Ph-C≡O$^+$).



10

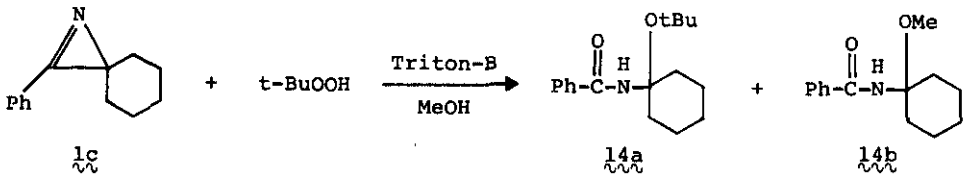
Treatment of 10 with 2,4-dinitrophenylhydrazine gave an orange solid, mp 163-6°, identical by ir to authentic acetaldehyde 2,4 dinitrophenylhydrazone and indicative of the acetaldehyde aminal structure of 10.

Since the lability of N-acylimines toward alcohols is well known,[7] it is reasonable to assume that 10 resulted from t-butanol addition to the precursor 11. The latter may have resulted from a ring opening of oxazabicyclobutane 12 as shown below:



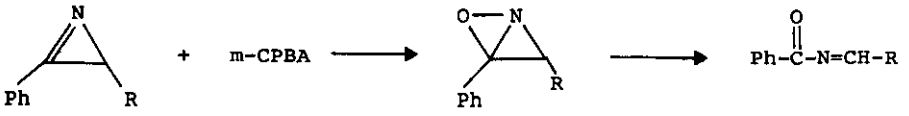
13 12 11

While azabicyclobutanes 4 usually undergo preferred ring opening at the center bond between the two rings, the weakest bond in 12 is expected to be the N-O bond. 3,3-Disubstituted azirines behave in the same manner. Thus, products 14, analogous to 10, were formed in the reaction of azirine 1c with t-butyl hydroperoxide in base.



1c 14a 14b

The intermediacy of N-ethylidenebenzamide 11 in the formation of 10 was ascertained by its isolation (59% yield) in the electrophilic exposidation of 1b with m-chloroperbenzoic acid (m-CPBA) in chlorobenzene. The structure of 11 was indicated by its mass spectrum (molecular ion at m/e 147 (38%), base peak at m/e 105 (Ph-C-)) and the nmr spectrum (methyl doublet at δ1.9 and six proton multiplet at 7.1-7.7). A similar reaction took place with azirine 1a.



1a, R:H
1b, R:Me

12

11a, R:H
11b, R:Me

Addition of t-butanol to 11b at room temperature or to the reaction mixture of 1b with m-CPBA led to the isolation of the t-butoxy ether 10. While the formation of 11 in the nucleophilic reaction of azirine 1 with t-butylperoxide anion can be explained by a decomposition[8] of 13 without invoking oxazabicyclobutane 12, its generation also in the electrophilic reaction with m-CPBA lends strength to the involvement of 12 as an intermediate[9] in these transformations. A similar intermediate is apparently involved in the M-CPBA oxidation of diazirines.[10]

EXPERIMENTAL

Reaction of 2-Phenyl-1-azirine with m-Chloroperoxybenzoic Acid. A solution of 200 mg (1.3 mmol) of 2-phenyl-1-azirine 1a and 0.24 g (1.4 mmol) of m-chloroperoxy benzoic acid in 20 ml of chlorobenzene was stirred magnetically and heated to reflux for 20 hr. The solution was washed with a 2 x 20 ml of saturated $NaHCO_3$ and the chlorobenzene was dried with anhydrous $MgSO_4$, filtered and the solvent was removed by distillation to give 98 mg (0.73 mmol) of N-methylenebenzamide 11a, as a colorless liquid.

Vapor phase chromatographic analysis on a 20% Carbowax column at 100°C showed one peak which was collected and analyzed by mass spectroscopy. Molecular ion peak at m/e 133 (41%); other peaks at m/e 105 (100%) and m/e 77 (35%). The nmr showed a multiplet at δ7.1-7.6.

Reaction of 2-Phenyl-3-methyl-1-azirine with m-Chloroperoxybenzoic Acid. A solution of 200 mg (1.3 mmol) of 2-phenyl-3-methyl-1-azirine 1b and 0.24 g (1.4 mmol) of m-chloroperoxybenzoic acid in 20 ml of chlorobenzene was stirred magnetically and heated to reflux for 20 hr. The solution was washed with a 2 x 20 ml of saturated $NaHCO_3$, the chlorobenzene layer was dried with anhydrous $MgSO_4$, filtered, and the solvent was removed by distillation to give 121 mg of N-ethylidenebenazmide 11b as a red oil. Vapor phase chromatographic analysis on a 20% Carbowax column at 100°C showed one peak which was collected and analyzed by mass spectroscopy. Molecular ion peak at m/e 147 (38%); other peaks at m/e 105 (100%) and m/e 77 (41%). The nmr (acetone-d6/CCl_4) showed a six proton multiplet at δ7.1-7.7 and a three proton doublet at δ1.9.

When 1 g (13 mmol) of t-butanol was added during the reaction, 1'-t-butoxyethylbenzamide 10 was separated by gc in 18% yield; treatment of 11 with t-butanol likewise produced 10.

General Procedure for the Reaction of 1-Azirines with t-Butyl Hydroperoxide in Triton B. To 1.31 g (10 mmol) of 2-phenyl-3-methyl-1-azirine 1b in 20 ml of benzene was added 1.2 ml (10.8 mmol) of t-butyl hydroperoxide. After addition of 0.4 g (2.3 mmol) of "Triton B" (40% in MeOH), the mixture was allowed to stand for a 24 hr period. The reaction mixture was then washed twice with 30 ml of water, dried with anhydrous $MgSO_4$, filtered and the benzene was removed under vacuum to give an oil which upon cooling to -10°C yielded 0.46 g (21%) of 1'-t-butoxyethylbenzamide 10. Recrystallization from diethyl ether/pentane provided further purification of this amide (mp 105-106°), nmr ($CDCl_3$) δ7.2-8 (five proton multiplet), δ5.9 (two proton wide singlet), δ6.8-7.2 (broad one proton singlet, replaced when D_2O was added), δ5.8-6.2 (one proton multiplet), δ1.48 (three proton doublet, J=6 Hz), and δ1.28 (nine proton singlet). IR (KBr) showed peaks at 3350, 1650 and 1535 cm^{-1}. Mass spectrum m/e (rel. intensity) 148 (40.5), 121 (1.2), 105 (100), 77 (29), 57 (4.0), 43 (9.0).

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33

Found: C, 70.66; H, 8.72; N, 6.35

The filtrate from recrystallization of 10 was allowed to stand at -10°C for seven days during which time 0.21 g/9% yield of 2,5-dimethyl-3,6-diphenylpyrazine precipitated.

Reaction of 0.46 g of 2-phenyl-3,3-pentamethylene-1-azirine with t-butyl hydroperoxide following the general procedure gave 0.57 g of a clear oil which on chromatography provided 45 mg of starting azirine, 170 mg of N-(1-t-butoxycyclohexyl)benzamide 14a, ir 3400 cm^{-1}(NH); 1655 and 1522 cm^{-1}(amide); nmr δ7.2-7.9 (m, 5H), δ6.36-6.68 (S broad, 1H), δ1.4-2.6 (m, 10H), δ1.28 (S, 9H), and 85 mg of N-(1-methoxycyclohexyl)benzamide 14b, ir 3340 cm^{-1}(NH); 1645 and 1530 cm^{-1}(amide); nmr δ7.3-7.9 (m, 5H), δ6.0-6.25 (S broad 1H), δ3.3 (S, 3H), δ1.18-2.5 (m, 10H); m/e 202 $(M-OMe)^+$.

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DEDICATION

Dedicated with great admiration to Professor Herbert C. Brown on the occasion of his 70th Birthday.

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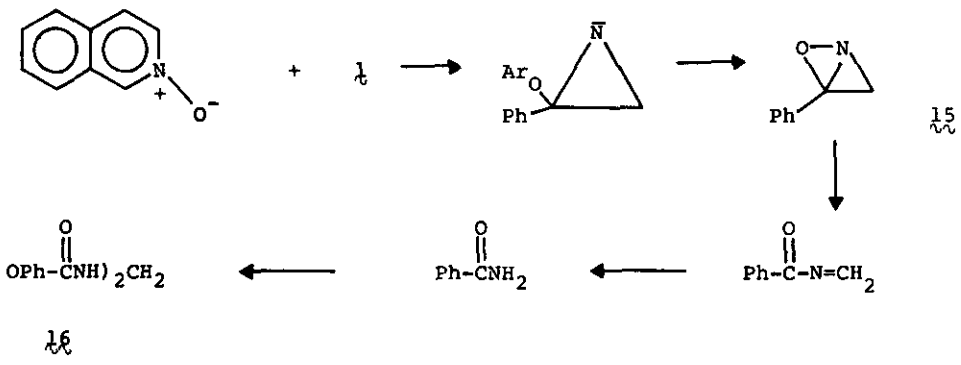

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