Proton-assisted Ring Opening of a 2,3-Dialkyl-4-alkylimino-1,2-oxazetidine

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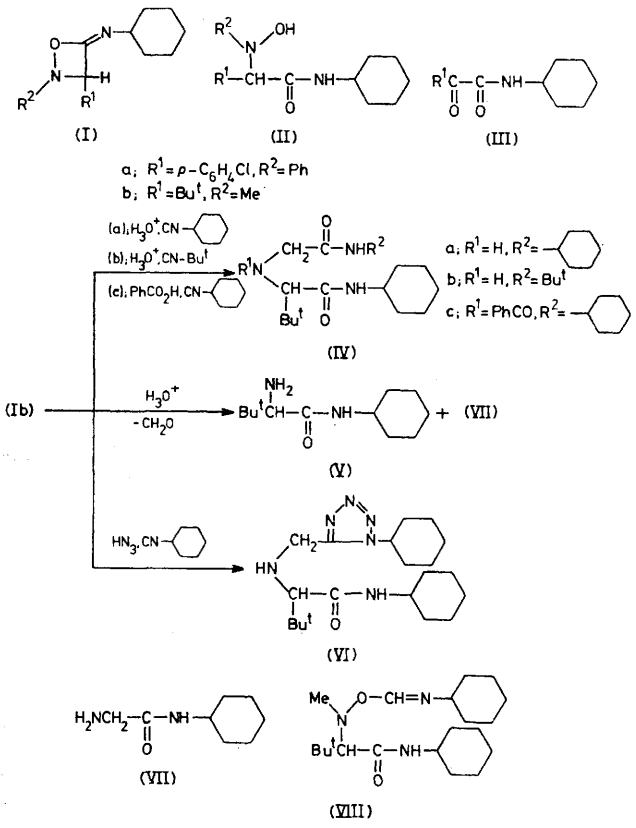
Summary 4-Cyclohexylimino-2-methyl-3-t-butyl-1,2-oxazetidine (Ib) prepared by BF_3-catalysed [3+1] cycloaddition of *N*-2,2-dimethylpropylidenemethylamine *N*-oxide (*C*-t-butyl-*N*-methyl nitrone) with cyclohexyl isocyanide is shown to give reactions of the hypothetical Schiff base from formaldehyde and the α-aminocarboxamide (V) when handled in acidic media.

APART from a polyfluorinated species,[1] the 4-imino-1,2-oxazetidine system in (I) does not as yet seem to have been isolated. The possible intermediacy of (I) in the BF_3-catalysed reaction of several aryl-substituted nitrones with isocyanides, *e.g.* (Ia), has been mentioned.[2] As one of the products of this reaction is the α-oxocarboxamide (IIIa), the supposed intermediate (Ia) must in part have undergone O–N bond cleavage with concomitant proton abstraction from position 3 to give the phenylimino compound corresponding to (IIIa) which was in turn hydrolysed.

This formal redox behaviour of the putative intermediate (Ia) aroused our interest in the reactivity of alkyl-substituted imino-oxazetidines such as (Ib) which, we felt, should



serve as a useful model for an understanding of the unexpected formation[3] of αα'-iminodicarboxdiamides (*e.g.*, IVa) from *N*-alkylhydroxylamines under the conditions of the Ugi reaction.[4]

Compound (Ib) could be synthesised in dry CH_2Cl_2 at −40 °C by short treatment (*ca.* 30 s) of the BF_3 complex of $Bu^tCH{=}N(O)Me$† (prepared *in situ*, 5% excess of nitrone) with 1·05 equiv. (based on BF_3) of cyclohexyl isocyanide and Et_3N (1 : 1). Immediate work-up (Na_2CO_3 soln.) afforded the [3 + 1] cycloadduct‡ (Ib), yellow oil; i.r. 1755s cm^{-1} (C=N), n.m.r. spectrum as expected, alkyl [δ ($CDCl_3$) 3·6—3·3 (1H, m), 2·98 (3H, s), 2·0—1·1 (10H, m), and 1·01 (9H, s)] and oxazetidine [δ 3·68 (1H, s)] resonances. On standing, the i.r. peak at 1755 cm^{-1} gradually weakened, while new absorptions appeared at 1670 and 1520 cm^{-1}. Attempts to purify (Ib) by distillation under reduced pressure resulted in spontaneous cleavage into cyclohexyl isocyanate and $Bu^tC{=}NMe$.§ Thermal degradation of 1,2-oxazetidines involving rupture of the O–N and C–C bonds is well established and generally accepted as a structure proof.

When freshly prepared (Ib) was treated with dilute mineral acid, a 50% yield of the α-aminocarboxamide (V)¶ (m.p. 138 °C) was obtained along with some of the glycine derivative (VII) (m.p. 90—92 °C, lit.,[5] m.p. 93—94 °C); the presence of formaldehyde was demonstrated by a common spot test. Remarkably, the hydroxylamine (IIb) could not be detected (this result is in contrast to ref. 2); the α-oxocarboxamide (IIIb) was also absent; *i.e.*, deprotonation as a consequence of O–N bond breaking occurred exclusively on the methyl substituent of (Ib), the hydrogen atom on C-3 remaining unaffected. Further reactions of (Ib) are in line with this observation. On adding aqueous HCl together with cyclohexyl and t-butyl isocyanides, respectively, (Ib) was converted into compounds (IVa)[3] (yield 60%) and (IVb)¶ (m.p. 178—179 °C, yield 30%). Accordingly, from a mixture of (Ib), cyclohexyl isocyanide, and benzoic acid the *N*-benzoyl derivative (IVc)¶ (m.p. 202 °C, yield 30%) was isolated, while with azide ion as nucleophile the tetrazole (VI)¶ (m.p. 123—125 °C, yield 30%) was produced.

These results clearly indicate that (Ib) is a possible intermediate in the synthesis of (IVa)[3] from *N*-methylhydroxylamine, pivalaldehyde, the isocyanide, and aqueous HCl. An alternative pathway *via* the *O*-imidoyl compound (VIII) which may be devised is considered unlikely for two reasons: first, α-additions of *NN*-disubstituted hydroxylamines to isocyanides leading to the general structure $R_2N{-}O{-}CH{=}N{-}R$ have not been reported and second, in our experience with *O*-acylated hydroxylamines closely related to (IIb),[6] a compound such as (VIII) when treated in acidic media should undergo β-elimination of *N*-cyclohexylformamide which is expected to involve proton loss from the position α to the carboxamide function, not from the *N*-methyl group.

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† B.p. 81—82 °C at 14 mmHg, n_D^{20} 1·4598; δ ($CDCl_3$) 6·75 (1H, s), 3·65 (3H, s), and 1·23 (9H, s) (W. Kliegel, personal communication).

‡ [3+1] Cycloadditions are still rare; those using isocyanides have been achieved with azomethine imines (J. A. Deyrup, *Tetrahedron Letters*, 1971, 2191), nitrile ylides (K. Burger and J. Fehn, *Angew. Chem. Internat. Edn.*, 1972, **11**, 47; K. Burger, J. Fehn, and E. Müller, *Chem. Ber.*, 1973, **106**, 1), and azomethine ylides (K. Burger, F. Manz, and A. Braun, *Synthesis*, 1975, 250) (*cf.* also J. A. Deyrup and G. S. Kuta, *J.C.S. Chem. Comm.*, 1975, 34).

§ Both compounds were identified by comparison (i.r. spectrum) with authentic samples.

¶ New compound, correct analysis obtained.

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