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ATTEMPTED GENERATION OF AZACYCLOPROPENONES A NEW ROUTE TO NITRILES[1]

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Abstract—A synthesis of the unknown azacyclopropenone (azirinone) system was attempted via α-azido ketenes. Treatment of α-azido acid chlorides with triethylamine, in an attempt to generate α-azido ketenes, led in good yield to nitriles containing one less carbon. At −60° it was possible to trap the α-azido ketene 7c with benzalaniline to form a β-lactam. The formation of nitriles most likely proceeds by intermediacy of an azirinone. The sequence of reactions provides a useful degradation of carboxylic acids to nitriles with loss of one carbon.

AZACYCLOPROPENONE (**1**) is a theoretically interesting molecule since it represents an example of a heretofore unknown heterocyclic system with 2π electron delocalization. Although Baeyer strain concepts would predict the highly strained cyclopropenones to be less stable that cyclopropanones, it was found that the latter are stable only in solution[2] while cyclopropenones can be isolated and stored.[3] These results have been attributed to the contribution of a zwitterionic form which would stabilize the molecule by 2π electron delocalization. A similar form **2** might be expected to

1 **2**

make azirinone (**1**) a Hückel aromatic system. On the other hand, though the azirinylium cation has been calculated to have approximately as much stabilization as the cyclopropenylium ion which has recently been synthesized,[3] attempts to prepare the aza system by hydride abstraction from an azirine have so far failed.[4] Furthermore, the opposing dipoles in azirinone (**1**) which are absent in cyclopropenone might be expected to destabilize the former.

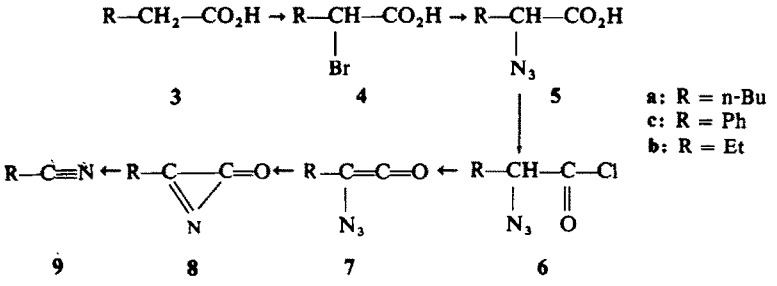
The availability of a general azirine synthesis by pyrolysis[5] or photolysis[6] of vinyl azides suggested an α-azido ketene* as a possible entry into the azirinone system. The regiochemistry[7] of addition of ICl to ketene to yield α-iodoacetyl chloride[9]

* After this work was essentially completed, we became aware of the report by A. K. Bose and coworkers (ref. 9) that α-azido ketenes can be generated from α-azido acid chlorides and trapped by means of Schiff bases. Brief mention of nitrile byproduct formation was also made.

precludes IN_3 addition to these systems as a route to α-azidoketenes, but a rather facile and mild procedure for the preparation of ketenes from acid halides is available[10] and was adapted to α-azido acid chlorides.

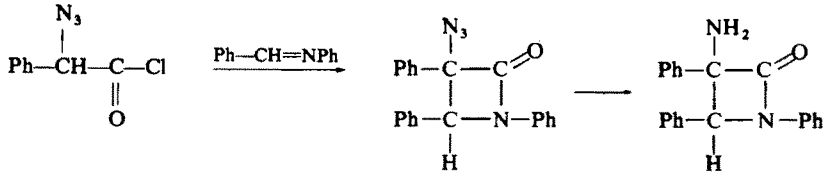
The preparation of α-azido acids **5** from α-halo acids **4** was best carried out using an equivalent of K_2CO_3 and an excess of sodium azide. Alternately displacement with NaN_3 was carried out on the α-bromo ester followed by base catalyzed hydrolysis to **5**.

SCHEME 1



Transformation to **6** was accomplished by means of thionyl chloride or oxalyl chloride, the latter usually giving a higher yield with less tar formation. The α-azido acid chlorides **6** were generally purified by vacuum distillation and treated with triethylamine in ether in the cold. This led to nitriles **9** as the only isolable product.

The formation of nitriles is best explained as shown in Scheme I. Attempts to trap the ketene **7** at 0° with benzalaniline were unsuccessful, but addition of Et_3N at −60° to **6c** followed by benzalaniline gave azetidinone **10** in 43% yield. Trapping



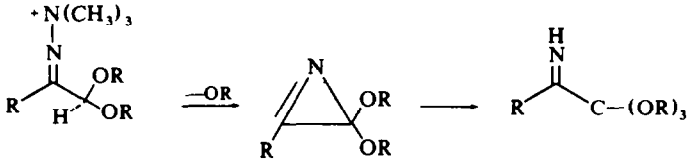
of such ketenes by Schiff bases has recently been reported; in fact **10** was thus obtained in 6% yield.[8] Azido lactam **10** was further characterized by catalytic reduction to 3-amino-1,3,4-triphenyl-2-azetidinin-11-one.

When azido ketene **7c** was generated at −60° and the mixture allowed to warm gradually, a color change from white to bright yellow was observed at about −20 to −30°. Apparently, **7** is thermally unstable above −30° and this accounts for the lack of reaction with benzalaniline at 0°.

Since ammonia, primary amines and secondary amines all yield amides when treated with an α-azido acid chloride[11] the initial reaction with Et_3N presumably proceeds via a quaternary acyl ammonium salt that decomposes to the α-azido ketene.

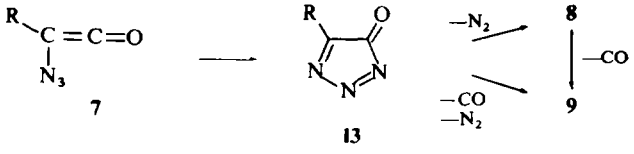
During the reaction of acid chloride **6a** with Et_3N two equivalents of gas (N_2 and CO) were produced, consistent with Scheme I. Azirinones (**8**) are apparently unstable

with respect to carbon monoxide and nitriles. The only other report that can be construed as an attempt toward the synthesis of an azirinone did not lead to the desired product; instead ring opening of the strongly polar intermediate **12** apparently took place.[12]

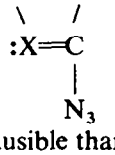


12

An alternate pathway that would account for the results reported here involves cyclization of the azidoketene **7** to triazolone **13**.* Concerted elimination of N_2 and CO or stepwise loss of N_2 to first give **8** could produce **9**. Though vinyl azides sometimes are converted to azirines even at 0°,[13] they usually do not cyclize to triazoles.



7 **13**

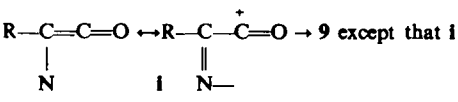
An exception is a report of formation of a stable triazole from β-tosyl vinyl azide which appears to involve carbanion formation at the β-carbon.[14] Other examples of triazole formation also involve an electron rich centre (i.e. **14** = N, S but not O) β-to the azido function.  **14**. On this basis we regard the intermediacy of an azirinone (**8**) as more plausible than that of **13** in the formation of nitriles.

Since the one step conversion of α-azido acid chlorides **5** to nitriles **9** proceeds in good yield and carboxylic acids **3** can readily be converted to **5** via α-bromo acids **4**, Scheme I represents a useful one carbon degradation of carboxylic acids.

EXPERIMENTAL

All m.ps were determined on a Fisher–Johns m.p. block and are uncorrected. IR spectra were obtained neat or in KBr on a Perkin–Elmer IR-21 spectrometer. NMR spectra were taken in $CDCl_3$ using TMS as an internal standard with either a A 60 or A 60A spectrometer. Microanalysis were performed by either A. Bernhardt, Mulheim, Germany or Gailbraith Laboratories, Knoxville, Tennessee. In NMR descriptions, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

Ethyl α-azidocaproate was prepared from ethyl α-bromocaproate and NaN_3 in aqueous EtOH 70% yield, b.p. 68°/7 mm; lit.[15] 66% yield, b.p. 93–95°/13–14 mm; IR 2119, 1754 cm^{-1}; NMR τ 5·75 (q), 6·2

* A further possibility involves **7** →  except that **i** is expected to close to azirine **8**.

(t, broad)„ 8–9·2 (m) rel. intensities: 2:1:12. *α-Azido caproic acid* (**5a**)[15] was obtained in 89% yield by KOH hydrolysis of the above ester at 25° for 3 hr; IR 4000–2500 (broad), 2119, 1733 cm^{-1}.

α-Azidocaproyl chloride (**6a**) was prepared by refluxing the above acid in $SOCl_2$ or $(COCl)_2$, distillation of excess acid chloride and then distillation of the residue under vacuum. Thionyl chloride gave a 77% yield and oxalyl chloride a 92% yield of colorless liquid, b.p. 48–50°/1·4 mm. Identified as its amide, from CH_2Cl_2/pentane, m.p. 53–53·5°; IR 3401, 3215, 2119, 1653, 1613 cm^{-1}. (Found: C, 46·31, H, 7·88. Calc. for $C_6H_{12}N_4O$: C, 46·14; H, 7·74%).

Treatment of α-azidocaproyl chloride (**6a**) *with* Et_3N. To a stirred solution of 5·27 g of acid chloride in 50 ml of anhyd ether was added dropwise a soln of 3·33 g of Et_3N in 50 ml of anhyd ether. The rate of addition was adjusted to a gentle reflux of the ether. Two equivalents of gas were evolved and measured. After 45 min the slurry was washed with water and extracted into ether. Upon removal of solvent there was obtained 2·28 g of **9a** identified by its IR and NMR spectra.

α-Azido butyric acid (**5b**). α-Bromocutyric acid (83·5 g) was exactly neutralized with 34·6 g K_2CO_3 in 750 ml H_2O. Immediately 65 g NaN_3 dissolved in 250 ml. H_2O was added. The flask was wrapped in aluminum foil and allowed to stand 48 hr at room temp. One mole of 10% HCl was added.

Extraction with ether, washing with H_2O and drying over $MgSO_4$ were followed by solvent removal *in vacuo* to yield 48·4 g (75%) of a pale yellow liquid; lit.[16] b.p. 81°/0·17 mm, detonates; IR 3600–2500, 2119, 1715 cm^{-1}, NMR τ 6·1 (t), 8·12 (q), 8·91 (t), rel. intensities, 1:2:3.

α-Azidobutylryl chloride (**6b**). The α-azido acid **5b** (12·9 g) was refluxed in 25 ml of $(COCl)_2$ for 3 hr and **6b** was distilled as a colorless oil, 12·66 g (86%), b.p. 64°/13 mm; IR 2119, 1792 cm^{-1}. Identified as its amide, m.p. 30–32°, lit.[16] m.p. 38–39°, IR 3200, 1680 cm^{-1}.

Treatment of α-azidobutyryl chloride with Et_3N. From 14·75 g of **6b** and 10·2 g of Et_3N in anhyd ether for 2 hr at room temp there was obtained a 95% yield of $Et_3N \cdot HCl$ and upon distillation through a 6" Vigreux column 2·2 g of colorless liquid (40%), identified as propionitrile **9b** by its IR and NMR spectra.

α-Azidophenylacetic acid (**5c**), was prepared as described[17] except that the NMR of the crude product indicated 70% α-azidophenylacetic acid and 30% mandelic acid. The best procedure to separate these was to repeatedly extract the solid with hot Skellysolve "B" and crystallize the residue from benzene to yield α-azidophenylacetic acid, m.p. 97–99°, lit,[17] 98·5°, IR 3600–2500, 2110, 1718 cm^{-1}, NMR τ 0·88 (s), 2·6 (s), 4·99 (s), rel. intensities 1:5:1.

α-Azidophenylacetyl chloride **6c**. α-Azidophenylacetic acid (1·77 g) was dissolved in 5 ml $(COCl)_2$ and refluxed for 4½ hr. The yield of crude **6c** was almost quantitative. Fractional distillation yielded 1·48 g (76%) of colorless oil, b.p. 94°/2 mm, IR 2119, 1786, 1248 cm^{-1}.

Treatment of α-azidophenylacetyl chloride with DABCO. A soln of 0·123 g of DABCO dissolved in 5 ml of ether was added to 0·195 g of **6c** in 2 ml of ether under N_2 in an ice-salt bath and stirred for 30 min. The slurry was filtered and the solvent was removed *in vacuo* to give a quantitative yield of crude benzonitrile which was clarified by passage through aluminum oxide to yield 85 mg (85%) of pure **9c** identified by its IR and NMR spectra.

3-Azido-1,3,4-Triphenylazetidinone (**10**). The ketene **7c** was generated as described above using 0·02 mole of **6c** and 0·02 mole of Et_3N at a temp of −60°. To the reaction mixture was added 3·6 g (0·02 mole) benzalaniline in 20 ml ether while keeping the temp below −50°. After the addition the mixture was allowed to warm to room temp (at about −25° the mixture turned a bright yellow). Water, 200 ml, was added and the ppt filtered and washed with EtOH until it was colorless. Recrystallization from EtOH provided 2·82 g (43·4%) silky needles, m.p. 160–161° (lit.[8] m.p. 160–161), IR 2110 and 1750 cm^{-1}. (Found: C, 74·05; H, 4·80; N, 16·70. Calc. for $C_{21}H_{16}N_4O$: C, 74·18; H, 4·74; N, 16·48%).

3-Amino-1,3,4-triphenyl-2-azetidinone (**11**). This compound was prepared by catalytic reduction of **10** with hydrogen and Adams' catalyst;[8] m.p. 170·9–171·0°. (Found: C, 80·06; H, 5·86; N, 8·70. Calc. for $C_{21}H_{18}N_2O$: C, 80·32; H, 5·78; N, 8·92%).

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