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INTERMEDIACY OF α-CHLORO AMIDES IN THE BASIC HYDROLYSIS OF α-CHLORO NITRILES TO KETONES

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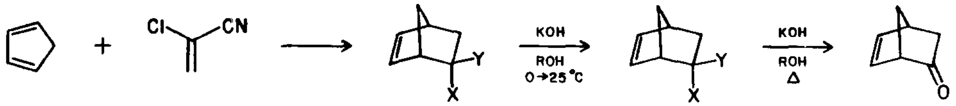
Summary: Isolable α-chloro amides are intermediates in the formation of ketones by basic hydrolysis of α-chloro nitriles. Possible mechanisms for the generation of ketones from α-chloro amides are discussed.

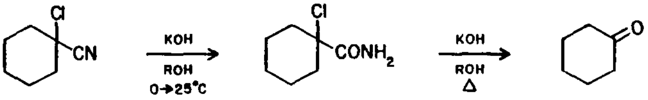
The formation of ketones by basic hydrolysis of α-chloro nitriles is well known in connection with the use of 2-chloroacrylonitrile as a Diels-Alder ketene equivalent.[1] This methodology generates formal [4+2] ketene cycloadducts of 1,3-dienes *via* Diels-Alder reaction with 2-chloroacrylonitrile, followed by hydrolysis (*e.g.*, eq. 1). No mechanistic studies of the hydrolysis step have previously been reported, although pathways involving nucleophilic displacement of chloride or cyanide, affording intermediate cyano- or chlorohydrins, have been proposed.[2] *A priori* we regarded both S_N2 and S_N1 displacements as improbable in these systems. We report here that under a variety of hydrolysis conditions, representative 2-chloroacrylonitrile Diels-Alder adducts as well as saturated α-chloro nitriles are initially converted to isolable α-chloro amides, which then are transformed to ketones (eq. 1 and 2). Possible mechanisms for the latter transformations are discussed.



(1)

1 X= Cl, Y= CN
2 X= CN, Y= Cl

3 X= Cl, Y= CONH$_2$
4 X= CONH$_2$, Y= Cl



(2)

6 7

Preparation of Intermediates. Diels-Alder reaction of cyclopentadiene and 2-chloroacrylonitrile smoothly affords an 80:20 mixture of α-chloro nitriles 1 and 2.[3] We were unable to separate 1 and 2 by any convenient preparative method.[4] However, mild hydrolysis (potassium hydroxide in alcohol solvents, 0→25°C; *vide infra*) gave a mixture of the corresponding α-chloro amides 3 and 4, from which multi-gram quantities of pure *endo*-chloro amide 3[5] were easily isolated by medium pressure liquid chromatography (mplc). Isomerically pure 1 was obtained by dehydration of 3 using trifluoroacetic anhydride and pyridine in tetrahydrofuran (0→25°C, 86% yield).[6]

The pure *exo*-chloro isomers were prepared from the Diels-Alder adducts of cyclopentadiene and acrylonitrile. Chlorination of the *endo*/*exo* adduct mixture using phosphorus pentachloride and pyridine in chloroform afforded a 94:6 mixture of **2** and **1**.[7] After hydrolysis to a mixture of α-chloro amides, pure *exo*-chloro amide **4**[5] was obtained *via* mplc. Dehydration as before gave pure *exo*-chloro nitrile **2**. In similar fashion cyanocyclohexane was readily converted to the α-chloro derivative **6**, which upon hydrolysis furnished the α-chloro amide **7**.[8]

Intermediacy of α-Chloro Amides in α-Chloro Nitrile Hydrolysis. α-Chloro nitriles **1** and **2** can be converted to 5-norbornen-2-one (**5**) under a variety of conditions. Suitable choice of reaction time and temperature permitted isolation of the corresponding α-chloro amides **3** and **4** after treatment of **1** or **2** with all hydrolysis reagent/solvent systems studied. Resubmission of the chloro amides to each reagent/solvent combination under more vigorous conditions (higher temperatures and/or longer times) then effected conversion to **5**.

The experiments leading to isolation of chloro amides **3** and **4** are summarized in Table I. The readily available 80:20 mixture of **1** and **2** (*vide supra*) was employed in initial studies. Treatment of the mixture with potassium hydroxide in various solvents at 0→25°C afforded the chloro amides **3** and **4**,[9] admixed in some cases with ketone **5**. Although the yield of chloro amides was not optimized for all solvents, increasing solvent polarity generally resulted in formation of greater amounts of **5**. Using ethanol as solvent, amide hydrolysis to the corresponding α-chloro acids was a significant side reaction.[10] Highest yields of α-chloro amides were realized using *t*-amyl alcohol as solvent; under these conditions the pure *endo*/*exo* isomers **1** and **2** were converted to **3** and **4**, respectively, with comparable efficiency (85-87% yields). No norbornenone could be detected in these reaction mixtures. 2-Chloroacrylonitrile Diels-Alder adducts have also been converted to ketones by treatment with sodium sulfide nonahydrate in refluxing ethanol.[11] Upon exposure to these reagents at 25°C, the mixture of **1** and **2** afforded the corresponding chloro amides in 68% yield.

Table I. Conversion of α-Chloro Nitriles 1 and 2 to α-Chloro Amides 3 and 4

Chloro nitrile	Reaction conditions	Yields(%) Chloro amide[a]	Norbornenone[b]	Chloro acid[a]
1 + **2** (80:20)	3 eq KOH/DMSO/25°/5 h	16	53	d
"	3 eq KOH/EtOH/0→25°/24 h	66	6	15
"	3 eq KOH/*t*-BuOH/25°/4 h	86	3	c
"	3 eq KOH/*t*-AmylOH/0→25°/5 h	87	c	c
"	3 eq $Na_2S \cdot 9H_2O$/EtOH/25°/68 h	68	e	d
1	3 eq KOH/*t*-AmylOH/0→25°/5 h	87	c	c
2	3 eq KOH/*t*-AmylOH/0→25°/6 h	85	c	c

[a] Isolated yield of **3** and/or **4**. [b] Gc yield using *p*-xylene as internal standard. [c] None detected. [d] Not analyzed for. [e] Present, yield not determined.

More vigorous base treatment of α-chloro amides **3** and **4** afforded norbornenone **5**. Highest yields of ketone were obtained using potassium hydroxide in *t*-butanol (Table II). *Endo*-chloro amide **3** reproducibly gave **5** in *ca*. 95% yield (gc) using these reagents (70°C, 5.5 h). The conversion of *exo*-chloro amide **4** to **5** was somewhat faster (65°C, 2 h), and also more capricious and less efficient (68-87% gc yields). Other bases can be employed in these transformations as well; for example, treatment of **3** with potassium *t*-butoxide in *t*-butanol at 75°C gave 5 in 90% yield (gc). Isolated yields of 5 are undoubtedly diminished by its volatility; treatment of 6 g of chloro amide (90:10 mixture of 3 and 4) with 2.2 eq of KOH in 60 ml of t-butanol at 75°C for 6 h afforded 5 in 71% yield after workup and distillation.

Table II. Conversion of α-Chloro Amides 3 and 4 to Norbornenone (5)

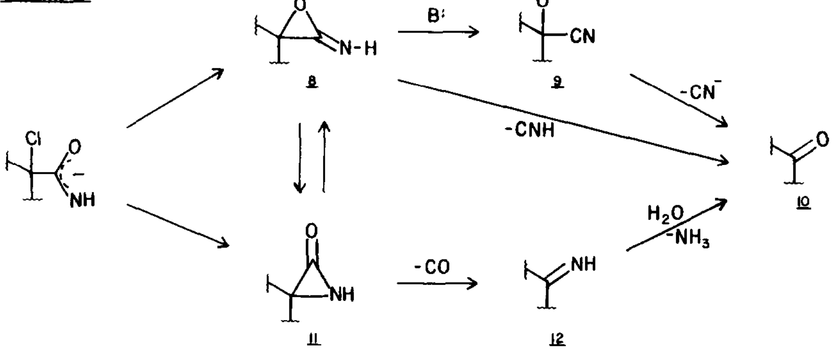
Chloro amide	Reaction conditions	Norbornenone yield (%)[a]
3	2.2 eq KOH/DMSO/25°/6 h	91
3	4.0 eq KOH/EtOH/80°/48 h	68
3	2.2 eq KOH/t-BuOH/75°/5.5 h	95
3	2.2 eq KO-t-Bu/t-BuOH/75°/4 h	90
4	2.2 eq KOH/t-BuOH/65°/2 h	68-87
4	2.2 eq KOH/t-AmylOH/65°/4 h	75

[a] Gc yield using p-xylene as internal standard.

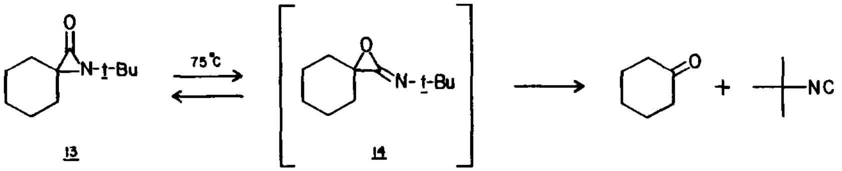
The saturated cyclohexane derivatives behaved similarly. Thus, hydrolysis of α-chloro nitrile 6 using 3 eq of potassium hydroxide in t-amyl alcohol (0→20°C, 12 h) afforded α-chloro amide 7 in 86% yield (isolated), together with cyclohexanone (ca. 7% yield by gc). Exposure of 7 to 2.2 eq of KOH in t-butanol (55°C, 6 h) produced cyclohexanone in 86% yield (gc).

Mechanism of Formation of Ketones from α-Chloro Amides. Possible pathways for the base-induced conversion of α-chloro amides to ketones are outlined in Scheme I. Displacement of chloride by the ambident amide anion could generate an imino oxirane 8 and/or an isomeric α-lactam 11. Base-induced fragmentation of 8 would afford ketone 10 via cyanohydrin anion 9. Alternatively, direct conversion of 8 to 10 could occur via expulsion of CNH. α-Lactam 11 could be converted to ketone 10 by loss of CO[12] to give imine 12, followed by hydrolysis. Interconversion of 8 and 11 may also be possible.

Scheme I



We have shown that the 11→12→10 pathway is not significant in the transformation of 3 or 4 to 5, since Liebig titration[13] reveals the formation of ca. one equivalent of CN⁻ in our reactions. We are unable to evaluate the contributions of the other processes shown in Scheme I, but several of the steps are analogous to known reactions. Base-induced cyclizations of α-halo secondary amides afford α-lactams in good yield,[14] but similar reactions of α-halo primary amides have apparently not been described. Sheehan, et al., have reported that α-lactam 13 affords cyclohexanone and t-butyl isocyanide upon warming to 75°C for 10 min (eq. 3).[15] They proposed that 13 is in equilibrium with its imino oxirane isomer 14,[16] which fragments to give the products. Imino oxiranes have been invoked as intermediates in other processes as well,[17] but to date these substances have eluded isolation and characterization.[18,19] Thus we are unaware of any precedent for the conversion of an α-chloro amide anion to an imino oxirane 8, or for the base-induced fragmentation of 8 to give a cyanohydrin anion 9, but these appear to be reasonable possibilities.[20]



(3)

We will soon describe new catalysts for Diels-Alder reactions of 2-chloroacrylonitrile which greatly enhance the usefulness of this dienophile as a ketene equivalent.

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Footnotes and References

1. For a review of Diels-Alder ketene equivalents, see S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *Synthesis*, 289 (1977).
2. P. K. Freeman, D. M. Balls, and D. J. Brown, *J. Org. Chem.*, 33, 2211 (1968).
3. J. Paasivirta and R. Kuusisto, *Suomen Kemistilehti B*, 40, 291 (1967).
4. 1 and 2 were previously separated by preparative gc and characterized: see ref. 3.
5. 3 and 4 were characterized by ^{1}H and ^{13}C nmr, ir, low resolution mass spectrometry, and elemental (C,H,N) analysis. Melting points (after recrystallization from ether-pentane; uncorrected): 3, 116-117°C; 4, 140-141°C.
6. F. Campagna, A. Carotti, and G. Casini, *Tetrahedron Lett.*, 1813 (1977).
7. H. Krieger and F. Nakajima, *Suomen Kemistilehti B*, 42, 314 (1969).
8. Alternative preparations of 6 and 7 have been described: C. L. Stevens and T. H. Coffield, *J. Amer. Chem. Soc.*, 73, 103 (1951).
9. Hydrolysis of nitriles to amides using KOH in *t*-butanol is ordinarily carried out at reflux: J. H. Hall and M. Gisler, *J. Org. Chem.*, 41, 3769 (1976). In the present cases the reaction presumably is accelerated by the electron-withdrawing α-chloro substituent.
10. The α-chloro acid isolated from hydrolysis of the 80:20 mixture of 1 and 2 appeared to be entirely the *endo*-chloro isomer. The *exo*-chloro acid is known to be very sensitive to base; *cf.*, ref. 3.
11. D. A. Evans, W. L. Scott, and L. K. Truesdale, *Tetrahedron Lett.*, 121 (1972).
12. Loss of CO from an α-lactam has been reported; see ref. 14, p. 29.
13. H. H. Willard, N. H. Furman, and C. E. Bricker, "Elements of Quantitative Analysis," 4th ed., D. Van Nostrand Co., Inc., Princeton, 1956, pp. 133-5.
14. For a review of α-lactam chemistry, see I. Lengyel and J. C. Sheehan, *Angew. Chem. Int. Ed. Engl.*, 7, 25 (1968).
15. Certain other α-lactams also fragment in this fashion; see ref. 14, and references cited therein.
16. An INDO study of this isomerization has been reported for the unsubstituted parent system: E. R. Talaty and M. E. Zandler, *J. Het. Chem.*, 12, 151 (1975).
17. See, for example, P. C. Ip, K. Ramakrishnan, and J. Warkentin, *Can. J. Chem.*, 52, 3671 (1974); T. Saegusa, N. Taka-ishi, and Y. Ito, *Bull. Chem. Soc. Japan*, 44, 1121 (1971); and references cited therein.
18. For reports of attempted syntheses of imino oxiranes, see G. L'abbé, *Angew. Chem. Int. Ed. Engl.*, 19, 276 (1980), and references cited therein.
19. Imino aziridines and an imino thiirane, respectively the nitrogen and sulfur analogs of imino oxiranes, have been isolated; see ref. 18.
20. Preliminary studies related to the work described herein were carried out by C.S.S. at Harvard University.

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