4,4-Diphenyl-1,2-oxazetidin-3-ones. Synthesis and Ring Fissions

TUVIA SHERADSKY, URI REICHMAN, AND MAX FRANKEL

Department of Organic Chemistry, The Hebrew University, Jerusalem, Israel

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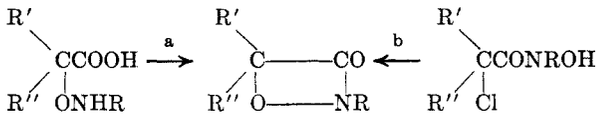
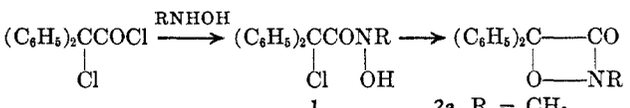
Five N-substituted 4,4-diphenyl-1,2-oxazetidin-3-ones were prepared by the reaction of α-chlorodiphenylacetyl chloride with N-substituted hydroxylamines. The ring fissions on electron impact, on hydrogenation, and on treatment with hydrogen chloride were studied.

The 1,2-oxazetidine system is of interest because of its structural relationship to β-lactams and to cycloserine. The first compound of this type was reported by Staudinger[1] who obtained 2,4,4-triphenyl-1,2-oxazetidin-3-one by the cycloaddition of diphenyl ketene and nitrosobenzene. This reaction was reinvestigated recently[2] and some additional 2,4,4-triaryl derivatives were prepared in 20–50% yield. The main disadvantage of the method was found to be the existence of a competing cycloaddition leading to the unstable 1,2-oxazetidine-4-ones; the latter are in certain cases the sole reaction products. On the other hand, a synthesis based on the ring closure of a four-membered chain would give one type of ring.

Two kinds of cyclization reactions can lead to the desired ring system: (a) ring closure at the amide bond (N–C-3) starting with α-aminooxy acids or their derivatives; (b) ring closure at the ether bond (O–C-4) starting with α-halohydroxamic acids, a method also suggested by Staudinger.[1]



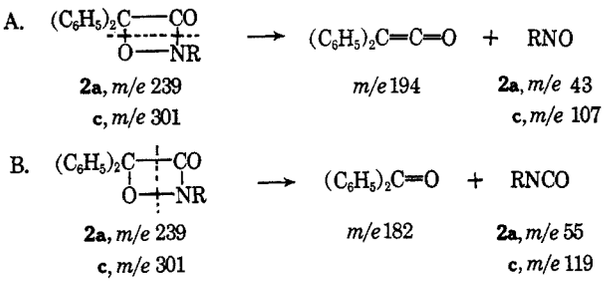
In this work we wish to report the synthesis of some compounds by route b. In the first series studied, the substituents were R′ = R″ = phenyl and R = aryl or alkyl. In this series the chlorine atom is in a benzhydrylic position and undergoes nucleophilic substitution very readily. Upon treating N-substituted hydroxylamines with chlorodiphenylacetyl chloride, the intermediate hydroxamic acids **1** could not be isolated and the oxazetidinones **2** were obtained directly.



2a, R = CH_3
b, R = C_6H_{11}
c, R = C_6H_{15}
d, R = *o*-$CH_3C_6H_5$
e, R = *p*-ClC_6H_5

The carbonyl absorptions of compounds **2** in the infrared spectrum are at the region to be expected for a strained four-membered ring (5.60–5.61 μ), at a wavelength slightly shorter than β-lactams, which are reported to absorb at 5.70–5.76 μ.[3] Molecular peaks corresponding to the right molecular weights were observed in the mass spectra. The main fragmentation processes were cleavages across the ring in the two directions. The four resulting ions—diphenylketene, acetophenone, the isocyanates, and the nitroso compounds—appeared in the spectra, for example in **2a** and **2c** (Scheme I).

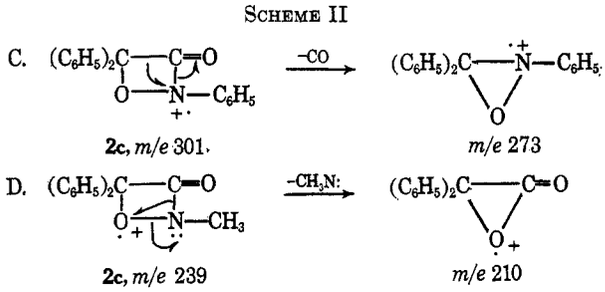
SCHEME I



A metastable peak corresponding to the departure of diphenylketene from the molecular ion appears in the spectrum of **2a** (calcd 157.3; obsd 157.5).

A significant point is revealed on comparing the mass spectra of **2c** and **2a**. The spectrum of **2c** shows a peak at M − 28 with a corresponding metastable peak (calcd 247.6; obsd 247.5), which accounts for a loss of CO from the molecular ion. The spectrum of **2a** does not show a peak at M − 28, but there is an intense one at M − 29 which accounts for a loss of N–CH_3. This can be interpreted on the basis of different locations of the positive charges in the fragmented ions. In **2c** the phenyl group stabilizes the positive charge on the nitrogen, whereas in **2a** charge stabilization by resonance interaction with aromatic rings is more likely to occur on the ring oxygen (Scheme II).

SCHEME II



Fragmentation process B occurs also on thermal decomposition; thus it is necessary to keep the inlet system at room temperature; otherwise only fragments of process B appear in the mass spectra.

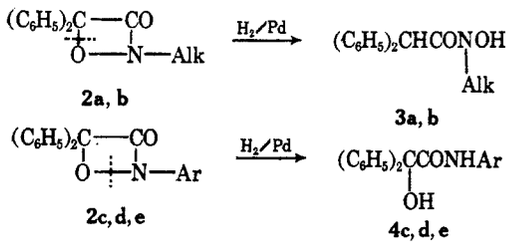
The influence of the nitrogen substituent upon the relative stabilities of the ring bonds is well exhibited in the course of the catalytic hydrogenation of compounds **2** (Scheme III).

Compounds **2a** and **2b** which have an aliphatic substituent on the nitrogen are cleaved upon catalytic hydrogenation at the C-4–O bond and the products are N-alkyldiphenylacetohydroxamic acids (**3**). In **2c**, **d**,

(1) H. Staudinger and S. Jelagin, *Chem. Ber.*, **44**, 365 (1911).
(2) G. Kresze and A. Trede, *Tetrahedron*, **19**, 133 (1963).
(3) J. A. Moore in "The Chemistry of Heterocyclic Compounds," Vol. 19, part 2, A. Weissberger, Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p 117.

and **e**, which have an aromatic substituent on the nitrogen, the N–O bond is cleaved and the products are benzilanilides (**4**). This difference can be explained on the basis of the inductive effects of the nitrogen substituents. In **2a** and **2b** the N–O bond is stabilized by electrons pushed toward it by the alkyl groups, while in **2c**, **d**, **e** the aromatic rings withdraw electrons from the N–O bond and it becomes the less stable one. The difference in the reaction course can also be caused by different forms of bonding of the two types of compounds to the catalyst surface.

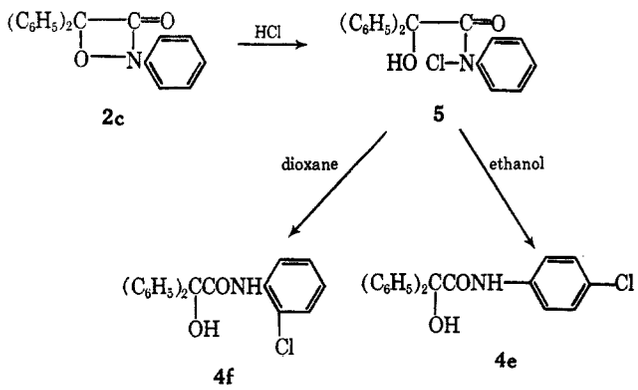
SCHEME III



The structures of the hydrogenation products were established by direct comparisons with authentic samples. The hydroxamic acids **3** were prepared from diphenylacetyl chloride and the appropriate hydroxylamine. Benzilanilides were obtained by hydrolysis of α-chlorodiphenylacetanilides.

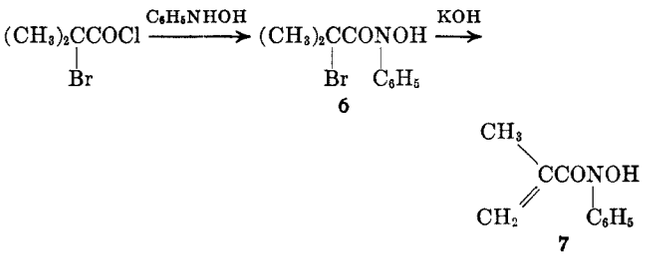
Staudinger[1] reported that treatment of **2c** with ethereal hydrogen chloride yielded a compound with mp 157.5–158.5°. On the basis of elemental analyses ($C_{20}H_{16}NO_2Cl$) he assigned to it the structure of 2-chloro-2,2,N-triphenylacetohydroxamic acid (**1c**) which is the intermediate, not isolable, but postulated in the synthesis reported here. We repeated the reaction using hydrogen chloride in ether or dioxane and obtained the identical compound (melting point and analyses). It could not be cyclized to **2c**. Its chlorine was very inert to nucleophilic reagents and it did not give a color reaction with $FeCl_3$. These observations point to the fact that Staudinger's structure assignment for this compound is incorrect. The infrared spectrum of it was very similar to those of the benzilanilides **4** obtained by hydrogenation. Direct comparison with an authentic sample showed it to be benzil-*o*-chloroanilide (**4f**). Treatment of **2c** with ethanolic hydrogen chloride yielded a different isomer (mp 212°) which was shown to be benzil-*p*-chloroanilide (**4e**) (Scheme IV).

SCHEME IV



The ring cleavage by hydrogen chloride thus occurs at N–O bond, the chlorine becoming attached to the less electronegative nitrogen, yielding the intermediate N-chlorobenzilanilide **5** which rearranges by the "Orton rearrangement,"[4] the chlorine migrating into the ring to the *ortho* position in nonhydroxylic solvents and to the *para* position in ethanol; by the same process, **2e** yielded benzil-2,4-dichloroanilide (**4g**).

An attempt was made to utilize the method for the synthesis of 4,4-dimethyl-1,2-oxazetidin-3-ones. Reaction of α-bromoisobutyryl chloride with N-phenylhydroxylamine yielded the stable α-bromo-N-phenylisobutyrohydroxamic acid **6**. Its treatment with bases led probably to β elimination rather than to cyclization. The oily product showed no absorption in 5–6-μ region and the presence of vinyl protons (δ 5.2) was observed in the nmr spectrum. Thus the expected oxazetidinone was not formed and the product probably consisted mainly of N-phenylmethacrylohydroxamic acid (**7**).



It appears that the synthesis of these compounds has to be approached by route a outlined in the introduction. This approach is now under study.

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 257 grating spectrophotometer. Mass spectra were obtained using an Atlas CH 4 mass spectrometer.

4,4-Diphenyl-2-methyl-1,2-oxazetidin-3-one (**2a**).—A mixture of N-methylhydroxylamine hydrochloride (2.49 g, 0.003 mol) and triethylamine (3 g) in 100 ml of dry ether was stirred for 40 min and α-chlorodiphenylacetyl chloride (2.65 g, 0.01 mol) in 50 ml of ether was added. After 6 hr of stirring the solution was filtered and evaporated. The oily residue solidified upon standing and was crystallized from ethyl acetate–petroleum ether (bp 40–60°) to give 2.2 g (90%) of **2a**: mp 82–85°; ir (Nujol), 1785 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 74.96; H, 5.40; N, 5.97.

2,4,4-Triphenyl-1,2-oxazetidine-3-one (**2c**).—A solution of 2.65 g (0.01 mole) of α-chlorodiphenylacetyl chloride in 60 ml of dry ether was added to a solution of N-phenylhydroxylamine (3.2 g, 0.03 mol) in 60 ml of dry ether. A precipitate of N-phenylhydroxylamine hydrochloride formed immediately and the mixture was stirred overnight. The salt was filtered off and the solution evaporated. The oily residue was dissolved in a small amount of benzene and chromatographed on neutral alumina (Merck, 60 g). Elution with petroleum ether (bp 40–60°) yielded a yellow oil which solidified. Crystallization from methanol yielded 1 g (33%) of **2c** as colorless plates: mp 73° (lit.[1,2] mp 73°); ir (Nujol), 1780 cm^{-1} (C=O).

In the same manner the reaction with N-cyclohexylhydroxylamine yielded **2b** (30%) [ir (neat), 1780 cm^{-1} (C=O)] and the reaction with N-*o*-tolylhydroxylamine yielded **2d** (60%) [ir (neat), 1785 cm^{-1} (C=O)]. Both compounds were obtained as viscous oils. Attempts to purify them further by distillation resulted in decomposition.

(4) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Reinehart and Wilson, New York, N. Y., 1962, p 650.

TABLE I
BENZILAMIDES $(C_6H_5)_2CCONHR$
OH

Compd	R	Registry no.	Mp, °C	Lit. mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Cl	Found, % C	Found, % H	Found, % N	Found, % Cl
4b	Cyclohexyl	17003-65-5	149		77.64	7.49	4.53		77.38	7.44	4.49	
4c	Phenyl		175	175[a]								
4d	*o*-Tolyl		147	147–148[b]								
4f	*o*-Chlorophenyl	17003-67-7	158		71.11	4.77	4.15	10.50	70.98	4.84	4.40	10.28
4e	*p*-Chlorophenyl		213	210–212[c]								
4g	2,4-Dichlorophenyl	17003-68-8	185		64.53	4.06	3.76	19.05	64.43	4.30	3.85	18.97
4h	3,4-Dichlorophenyl	17003-66-6	242		64.53	4.06	3.76	19.05	64.39	4.19	3.98	19.21

[a] H. Klinger, *Ann.*, **389**, 257 (1912). [b] P. A. Petyunin, I. S. Berdinskii, and N. G. Punferova, *Zh. Obshch. Khim.*, **27**, 1901 (1957); *Chem. Abstr.*, **52**, 4647 (1958). [c] P. A. Petyunin and A. S. Pesis, *Zh. Obshch. Khim.*, **26**, 233 (1956); *Chem. Abstr.*, **50**, 13955 (1956).

4,4-Diphenyl-N-*p*-chlorophenyl-1,2-oxazetidine (**2e**) was prepared as **2c** above from 4.3 g of N-*p*-chlorophenylhydroxylamine. A solid product was obtained directly and was crystallized from ethanol. The yield was 1.7 g (50%); mp 79°; ir (Nujol), 1785 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{14}NO_2Cl$: C, 71.53; H, 4.20; N, 4.17; Cl, 10.23. Found: C, 71.41; H, 4.20; N, 4.13; Cl, 10.23.

N-Methyldiphenylacetohydroxamic Acid (**3a**).—Solutions of N-methylhydroxylamine hydrochloride (0.835 g, 0.01 mol) and potassium hydroxide (0.56 g, 0.01 mol) in water (20 ml) and of diphenylacetyl chloride (1.15 g, 0.005 mol) in chloroform (60 ml) were vigorously stirred together for 4 hr. The layers were separated and the chloroform was dried ($MgSO_4$) and evaporated. The residue was crystallized from ethyl acetate–petroleum ether. Recrystallization from 50% methanol yielded 1.1 g (85%) of **3a** as a hydrate, mp 73°.

Anal. Calcd for $C_{15}H_{15}NO_2 \cdot H_2O$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.40; H, 6.64; N, 5.33.

N-Cyclohexyldiphenylacetohydroxamic Acid (**3b**).—To a solution of diphenylacetyl chloride (1.15 g, 0.005 mol) in ether (50 ml) N-cyclohexylhydroxylamine (1.15 g, 0.01 mol) in 50 ml of ether was added. The mixture was stirred for 5 hr, filtered, and evaporated. Crystallization from 50% methanol yielded **3b** (1.4 g, 90%), mp 182°.

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.40; H, 7.69; N, 4.41.

N-Phenyldiphenylacetohydroxamic acid (**3c**) was prepared in 90% yield as **3b** above: mp 159–160°.

Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 78.85; H, 5.60; N, 4.83.

N-*p*-Chlorophenyldiphenylacetohydroxamic acid (**3e**) was prepared in 95% yield: mp 175°.

Anal. Calcd for $C_{20}H_{16}NO_2Cl$: C, 71.11; H, 4.77; N, 4.15; Cl, 10.50. Found: C, 71.43; H, 4.58; N, 4.30; Cl, 10.38.

Benzilanilides (**4**).—These were prepared according to the following general procedure. A solution of α-chlorodiphenylacetyl chloride (1.33 g, 0.005 mol) and the appropriately substituted aniline (0.01 mol) in ether (80 ml) was stirred for 5 hr, filtered, and evaporated. Water (50 ml) was added to the residue and the mixture was heated under reflux for 5 hr and cooled. The anilides **4** were collected by filtration and crystallized from dilute ethanol. Yields were 90–95%. The compounds prepared are listed in Table I.

Catalytic Hydrogenation of Compounds 2.—The oxazetidinones **2** (0.01 mol) were dissolved in ethanol (50 ml). A catalyst (10% Pd/C, 200 mg) was added and the mixture was hydrogenated at 50 psi for 6 hr. The catalyst was filtered off and the solvent was evaporated. The products were crystallized from dilute ethanol. Yields were 90–95%. Compounds **2a** and **2b** yielded **3a** (mp 73°) and **3b** (mp 182°), respectively. Compounds **2c**, **2d**, and **2e** yielded **4c** (mp 175°), **4d** (mp 147°), and **4e** (mp 212°), respectively. Identity of the hydrogenation products with the authentic compounds described above was established by mixture melting point and ir spectra.

Reaction of 2c with Hydrogen Chloride. A. In Dioxane.—Compound **2c** (0.5 g) was dissolved in a 5% solution of HCl in dioxane (30 ml). After standing overnight, the solution was evaporated and the residue was crystallized from dilute ethanol affording **4f** (0.5 g), mp 157–158°. Mixture melting point with an authentic sample of **4f** gave no depression and the ir spectra were identical.

B. In Ethanol.—A solution of **2c** (0.5 g) in ethanolic HCl (5%, 30 ml) was refluxed for 5 hr. Evaporation and crystallization yielded **4e** (0.5 g), mp 212°, which was identical with the authentic material (ir spectrum and mixture melting point).

Reaction of 2e with Hydrogen Chloride.—In dioxane or ethanol as described above yielded **4g**, mp 185°, in both solvents. The products were identical with authentic **4g**.

α-Bromo-N-phenylisobutyrohydroxamic Acid (**6**).—A solution of α-bromoisobutyryl chloride (9.3 g, 0.15 mol) and N-phenylhydroxylamine (10.9 g, 0.3 mol) in dry ether (100 ml) was stirred at room temperature for 5 hr, filtered, and washed with water. Evaporation and crystallization from ethyl acetate–petroleum ether (bp 40–60°) yielded 7 g (53%) of **6**, mp 94°.

Anal. Calcd for $C_{10}H_{12}NO_2Br$: C, 46.53; H, 4.69; N, 5.43. Found: C, 46.35; H, 4.79; N, 5.10.

Treatment of **6** with ethanolic KOH or with triethylamine in benzene yielded oils which gave positive tests with $FeCl_3$ solution. Spectral evidence (see text) indicates that they consist mainly of N-phenylmethacrylohydroxamic acid (**7**).

Registry No.—**2a**, 17003-56-4; **2b**, 17003-57-5; **2c**, 17003-58-6; **2d**, 17003-59-7; **2e**, 17003-60-0; **3a**, 17003-61-1; **3b**, 17003-62-2; **3c**, 17003-63-3; **3e**, 17003-64-4; **6a**, 17003-69-9.