Reactions of 2,2-Dialkoxy Ketone Oximes with Chlorine and Bromine. Halogenation vs. Beckmann Fragmentation

Bryce C. Oxenrider and Milorad M. Rogić*

Corporate R&D Laboratories, Allied Corporation, Morristown, New Jersey 07960

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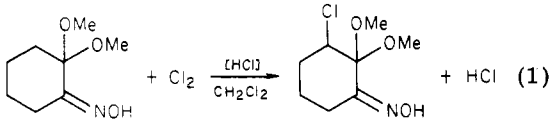
Reactions of 2,2-dialkoxycycloalkanone oximes with chlorine or bromine can be directed either to give 3-chloro- or 3-bromo-2,2-dialkoxycycloalkanone oximes or to undergo Beckmann fragmentation to give ω-(alkoxycarbonyl)alkanehydroximoyl halides. The resulting hydroximoyl halides can be converted either to the corresponding nitrile oxides, furoxane derivatives, or they could be rearranged through the intermediacy of nitrile oxides into corresponding isocyanates. Catalyzed Beckmann fragmentation of 3-chloro-2,2-dimethoxycyclohexanone oxime provided methyl 2-chloro-5-cyanovalerate, a useful lysine precursor.

Addition of methyl nitrite to a carbon–carbon double bond of ketone enol ethers is an efficient method for syntheses of 2-nitroso ketone acetal dimers as well as of the corresponding 2-oximino ketone acetals.[1] A mild catalytic Beckmann fragmentation of either of these substrates derived from C_5, C_6, C_8, C_{12}, and other cyclic ketones provided a convenient method for preparation of the corresponding ω-cyanoalkyl acid esters, which previously were not always readily available.[1,2] In effect, these transformations represent mild alternatives to the typical Beckmann conditions which generally require strongly acidic or highly reactiye acylating reagents.[3,4] This approach appeared particularly useful for the transformation of cyclic ketone derivatives, where α-oximino ketones were previously extremely difficult to prepare.[5,6]

In the present paper we describe still another useful transformation of 2-oximino ketone acetals. Reactions of 2-oximino ketone acetals (2,2-dialkoxy ketone oximes) with halogenating reagents can be directed either to give the corresponding 3-halo-2,2-dialkoxy ketone oximes or to undergo Beckmann fragmentation to give either ω-(alkoxycarbonyl)alkanehydroximoyl halides, ω-(alkoxycarbonyl)alkanenitrile oxides, or the corresponding furoxane derivatives.

Results and Discussion

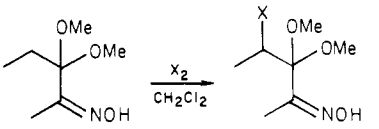
(1) Acid-Catalyzed Halogenations. Addition of gaseous chlorine to a solution of 2,2-dimethoxycyclohexanone oxime (1) in methylene chloride containing a catalytic quantity of dry hydrogen chloride led to the formation of 3-chloro-2,2-dimethoxycyclohexanone oxime **2** as the hydrochloride[7] (eq 1). Under similar conditions the reaction



(1)

1 2

Table I. Reactions of 2,2-Dialkoxy Ketone Oximes with Halogens[a]

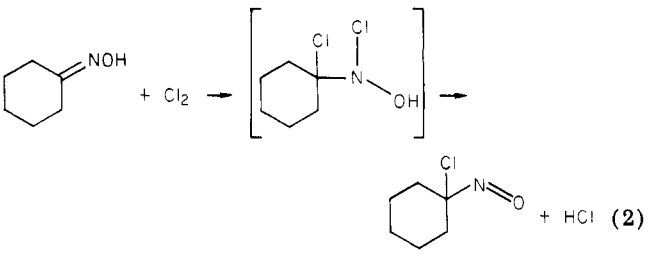


dimethoxy ketoxime (mmol)	X_2 (mmol)	yield, %
cyclohexanone (100)	Cl_2 (105)	96
cyclohexanone (10)	SO_2Cl_2 (12)	95
cyclohexanone (50)	Br_2 (53)	94
4-*tert*-butylcyclohexanone (20)	Cl_2 (21)	87
cyclooctanone (25)	Cl_2 (25)	90
cyclooctanone (25)	Br_2 (25)	~50
cyclododecanone (25)	Cl_2 (25)	~50
4-heptanone (25)	Cl_2 (25)	~62

[a] For a detailed experimental procedure, see the Experimental Section.

with bromine provided the corresponding bromo derivative. The reaction with sulfuryl chloride proceeded with the liberation of sulfur dioxide and also gave **2** in a comparable yield. Other substrates derived from 4-*tert*-butylcyclohexanone, cyclooctanone, and cyclododecanone as well as from open-chain ketones, for example, the 4,4-dimethoxy-3-heptanone oxime derived from 4-heptanone, behaved similarly. The results are summarized in Table I.

Reaction of the cyclohexanone oxime itself with chlorine proceeds readily and affords deep blue 1-nitroso-1-chlorocyclohexane,[8] which is stable toward further chlorination (eq 2). This reaction produces 1 equiv of hydrogen chloride which apparently does not affect the reaction. Presumably, an electrophilic attack of chlorine at



(2)

(1) Klein, K. P.; Demmin, T. R.; Oxenrider, B. C.; Rogić, M. M.; Tetenbeum, M. T. *J. Org. Chem.* **1979**, *44*, 275.
(2) Rogić, M. M.; Vitrone, J.; Swerdloff, M. D. *J. Am. Chem. Soc.* **1977**, *99*, 1156.
(3) Werner, A.; Piguet, A. *Chem. Ber.* **1904**, *37*, 4295. Werner, A.; Defscheff, T. *Ibid.* **1905**, *38*, 69. Blatt, A. H.; Barnes, R. P. *J. Am. Chem. Soc.* **1934**, *56*, 1148. Autrey, R. L.; Scullard, P. W. *Ibid.* **1965**, *87*, 3284. Hill, R. A. *J. Org. Chem.* **1962**, *27*, 29. Ohno, M.; Neruse, N.; Torimitsu, S.; Teresawa, I. *J. Am. Chem. Soc.* **1966**, *88*, 3168.
(4) For a general discussion of fragmentation reactions, see for example: Grob, C. A. "Theoretical Organic Chemistry, Report on the Kekule Symposium"; Butterworths: London, 1958; p 114; *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.
(5) Touster, O. *Org. React.* **1953**, *7*, 327–377.
(6) Ferris, A. F.; Johnson, G. S.; Gould, F. E. *J. Org. Chem.* **1960**, *25*, 496.
(7) This product was prepared earlier by methanolysis of 2,3-dichloro-2-methoxycyclohexanone oxime: Rogić, M. M.; Mares, F. U.S. Patent 3928445, 1975.
(8) Rheinboldt, H.; Dewald, M. *Justus Liebigs Ann. Chem.* **1927**, *455*, 305.
(9) In order to convert 2-methoxy-3-oximidocyclohexene into 2,3-dichloro-2-methoxycyclohexanone oxime by reaction with chlorine, the free base had to be converted first into the corresponding hydrochloride.[7]

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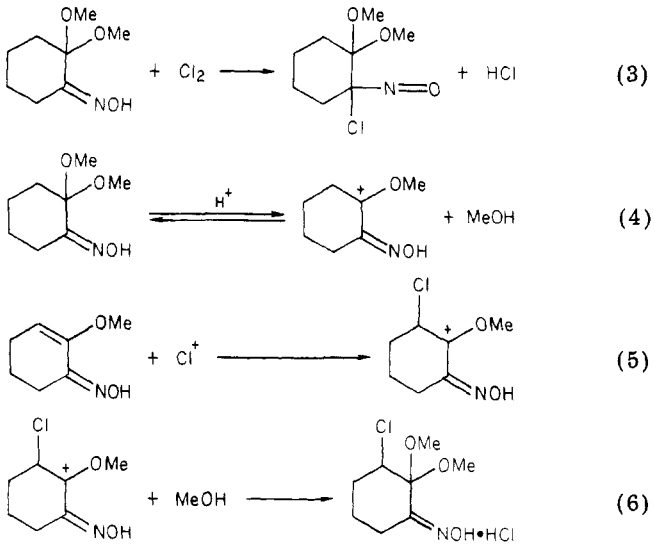
Scheme I

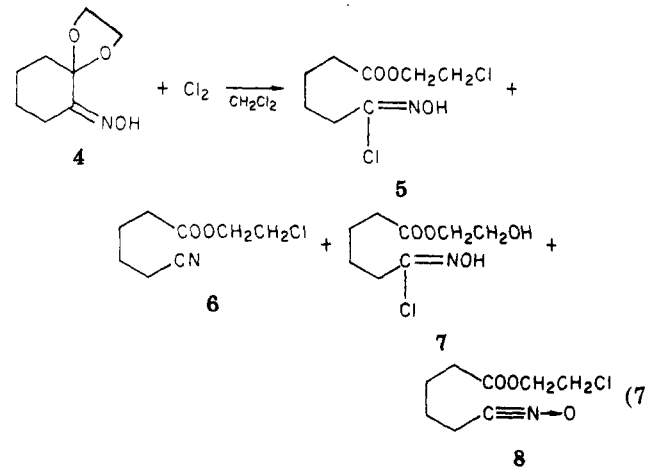


the oxime nitrogen followed by the reaction of the chloride anion at the carbon and subsequent elimination of hydrogen chloride summarizes the mechanism of this reaction.

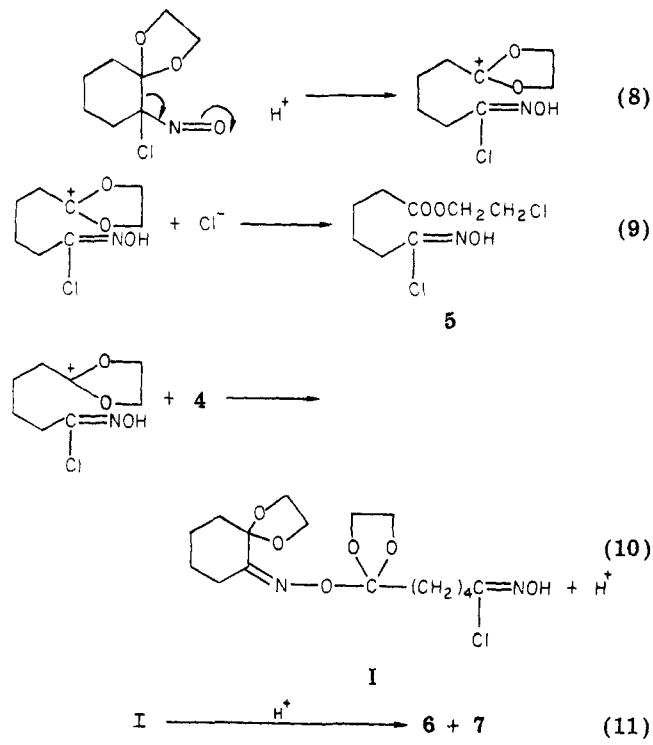
In the case of 2,2-dialkoxy ketone oximes, the reaction with chlorine would be expected to proceed analogously. However, hydrogen chloride liberated during the formation of, for example, the expected 1-nitroso-1-chloro-2,2-dimethoxycyclohexane from **1** (eq 3, Scheme I) can catalyze generation of 2-methoxy-3-oximidocyclohexene (**3**, eq 4). It appears that once generated the enol ether **3** reacts with chlorine more readily than the substrate itself. Presumably, electrophilic attack of chlorine at the carbon–carbon double bond of the enol ether **3** provides the C_2 carbonium ion intermediate (eq 5) that then reacts with methanol formed earlier from **1** to give the 3-chloro-2,2-dimethoxycyclohexanone oxime **2** (eq 6). The product then ties up the excess of hydrogen chloride as the hydrochloride of **2** (Scheme I). The protonation of the oxime group both in the substrate (e.g., **1**), as well as in the product (e.g. **2**), by the initially generated hydrogen chloride apparently does not preclude further generation of the enol ether intermediate required for the completion of the reaction. Because the acid catalyst can be generated by the initial reaction of the halogen with the oxime group, it is actually not essential to add the acid catalyst before introduction of halogen, but in most instances it is advantageous to do so.

(2) Beckmann Fragmentation of the 2,2-Dialkoxy Ketone Oximes with Halogens. Somewhat unexpectedly, the reaction of chlorine with 6-oximino-1,4-dioxaspiro[4.5]decane (**4**), a cyclic analogue of **1**, did not give any of the expected 10-chloro derivative. Instead, the reaction provided 5-[(2-chloroethoxy)carbonyl]pentanehydroximoyl chloride (**5**), which was accompanied by smaller quantities of 5-[(2-chloroethoxy)carbonyl]pentanenitrile (**6**), 5-[(2-hydroxyethoxy)carbonyl]pentanehydroximoyl chloride (**7**), and 5-[(2-chloroethoxy)carbonyl]pentanenitrile oxide (**8**, eq 7). The presence of the three minor products **6-8** was deduced from spectral evidence obtained on the total reaction mixture.

The outcome of this particular reaction suggests that the lifetime of the carbonium ion intermediate formed in the acid-catalyzed opening of the cyclic ketal moiety was much shorter than the lifetime of the corresponding methoxy analogues in eq 4. Consequently, concentration of the expected enol ether, 2-(2-hydroxyethoxy)-3-oximidocyclohexene, never became significant, and the reaction



Scheme II

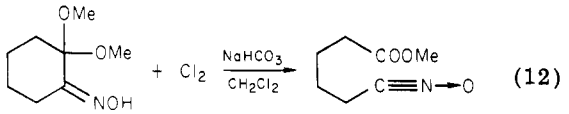


of chlorine with the carbon–carbon double bond is not observed. Instead, chlorine attacks the carbon–nitrogen double bond of the oximido group, just as in the case of cyclohexanone oxime itself, and provides the corresponding 1-chloro-1-nitroso intermediate. The liberated hydrogen chloride then catalyzes Beckmann fragmentation of this intermediate as indicated in Scheme II. Clearly, as it may be expected, protonation of the oxime nitrogen of the α,α-dialkoxy oximes is not a sufficient condition in itself to prevent reaction of the oxime nitrogen with electrophilic chlorine.

The fact that besides **5** smaller quantities of **6** and **7** were also formed indicates that the attack of the chloride anion at the alkoxy carbon of the dialkoxycarbonium ion intermediate (eq 9) was more efficient than the competing reaction of the carbonium ion center with the nucleophilic oxygen of the substrate's oxime group (eq 10 and 11), which would lead to the formation of the equimolar quantities of **6** and **7**.

According to the mechanism for the Beckmann fragmentation of **4** in Scheme II, even dimethoxy and other dialkoxy oximes should undergo the carbon–carbon bond cleavage with halogens to give ω-(alkoxycarbonyl)alkane-

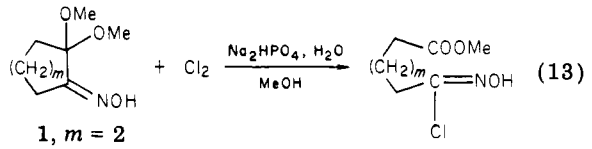
hydroximoyl halides, provided that the generation of the corresponding enol ether intermediates (e.g., eq 4) is suppressed. Clearly, this should be possible to accomplish either in a more basic solvent that could "buffer" the acid-generated from the initially produced dichloro intermediate (eq 3) or in the presence of a suitable base that would fulfill the same role. Indeed, the addition of chlorine to a solution of 2,2-dimethoxycyclohexanone oxime (1) in methylene chloride in the presence of an excess of anhydrous sodium bicarbonate proceeded with the evolution of carbon dioxide to give 5-(methoxycarbonyl)valeronitrile oxide (9, eq 12). Moreover, carrying out the same reaction



(12)

1 9

in methanol in the presence of an excess of disodium phosphate and 1 molar equiv of water allows isolation of 5-(methoxycarbonyl)valerohydroximoyl chloride (10) before significant formation of 9 occurs (eq 13). 2,2-Di-

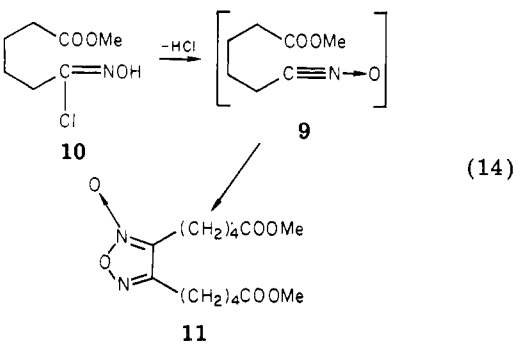


(13)

1, m = 2
12, m = 4

10, m = 2
13, m = 4

methoxycyclooctanone oxime (12) behaved similarly and gave 7-(methoxycarbonyl)heptanehydroximoyl chloride (13, eq 13). The hydroximoyl chloride 10 loses hydrogen chloride spontaneously on standing at room temperature and affords the corresponding furoxan 11 which is evidently formed by the dimerization of the intermediate nitrile oxide[10] 9 (eq 14). Both substrates 1 and 12 reacted

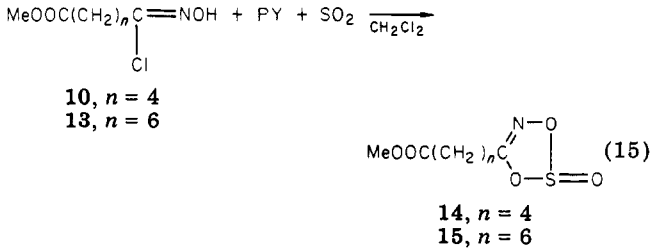


(14)

10 9 11

with bromine analogously and gave the corresponding bromo derivatives.

Treatment of the hydroximoyl chlorides or bromides with 1 molar equiv of pyridine and sulfur dioxide in methylene chloride gave the corresponding complexes of nitrile oxides with sulfur dioxide[11] (14 and 15, eq 15).

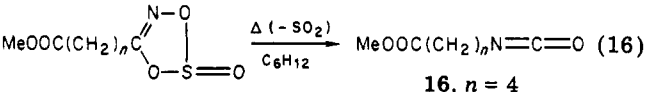


(15)

10, n = 4
13, n = 6

14, n = 4
15, n = 6

Heating of these complexes in refluxing cyclohexane led to the liberation of sulfur dioxide and rearrangement to the corresponding isocyanates[12] 16 and 17 (eq 16).

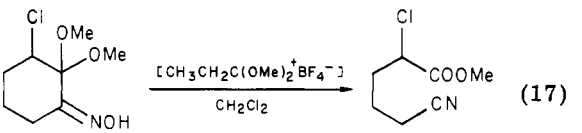


(16)

14, n = 4
15, n = 6

16, n = 4
17, n = 6

Earlier we prepared 3-chloro-2,2-dimethoxycyclohexanone oxime (2) by reaction of 2,3-dichloro-2-methoxycyclohexanone oxime with methanol.[7] At that time we converted 2 to a convenient lysine precursor methyl 2-chloro-5-cyanovalerate (18) using typical Beckmann conditions and 1 molar equiv of thionyl chloride as a cleavage reagent. The Beckmann fragmentation of 2 can also be carried out under catalytic conditions.[1] Thus, addition of a catalytic quantity of ethyldimethoxycarbonium tetrafluoroborate[1] to a solution of 2 in methylene chloride at room temperature caused an exothermic reaction that produced methyl 2-chloro-5-cyanovalerate (18) in a high yield (eq 17).



(17)

2 18

Conclusions

Earlier it was shown that 2,2-dialkoxycycloalkanone oximes undergo catalyzed Beckmann fragmentations under very mild reaction conditions to give previously difficult to obtain ω-cyano carboxylic acid esters.[1,2] This report demonstrated that the reactions of 2,2-dialkoxycycloalkanone oximes with chlorine or bromine can be directed either to give 3-chloro- or 3-bromo-2,2-dialkoxycycloalkanone oximes or to undergo Beckmann fragmentation to give ω-(alkoxycarbonyl)alkanehydroximoyl halides. The resulting hydroximoyl halides can be converted either to the corresponding nitrile oxides, furoxane derivatives, or rearranged through the intermediacy of nitrile oxides into corresponding isocyanates. Catalyzed Beckmann fragmentation of 3-chloro-2,2-dimethoxycyclohexanone oxime provided methyl 2-chloro-5-cyanovalerate, which was previously converted to methyl 2,6-diaminocaproate,[7] a useful lysine derivative.

Experimental Section

The reported melting points are uncorrected. The ^{1}H NMR, ^{13}C NMR, and infrared spectra were recorded respectively on Varian T60-A and CFT-20 instruments and on a Perkin-Elmer 128 spectrometer. Routine chemical-ionization mass spectra were obtained on a Finnigan 3100D mass spectrometer, while high-resolution mass spectra were obtained on an AEI MS 902 instrument.

The starting 2,2-dialkoxy ketone oximes were prepared by previously published procedures.[1,2] All the solvents were distilled prior to use.

The typical reaction vessel was a three-necked flask fitted with a condenser, magnetic stirring bar, thermometer, and gas-inlet tube and was protected by a dry nitrogen atmosphere.

2,2-Dimethoxy-3-chlorocyclohexanone Oxime (2). (a) Reaction with Chlorine. To a solution of 2,2-dimethoxycyclohexanone oxime (1; 17.3 g, 100 mmol) in 100 mL of dry methylene chloride containing about 0.1 g of anhydrous hydrogen

(10) For the dimerization and other chemistry of nitrile oxides see: Grundmann, C., Grunanger, P. "The Nitrile Oxides"; Springer-Verlag: New York, 1971, and references therein.

(11) Burk, E. H.; Carlos, D. D. *J. Heterocycl. Chem.* **1970**, *7*, 177.

(12) Barnes, J. F.; Paton, R. M. *J. Chem. Soc., Chem. Commun.* **1978**, 113.

chloride was introduced a slow stream of chlorine gas (7.5 g, 105 mmol) so that the reaction temperature did not exceed 35 °C. After being stirred at room temperature for 30 min, the reaction mixture was cooled to ~5 °C and diluted with 50 mL of cold water. Sodium carbonate (5.8 g, 55 mmol) was added in small portions to adjust the pH to 8. The organic layer was washed with cold water (50 mL), and after the mixture was dried, the solvent was evaporated at room temperature. The 2,2-dimethoxy-3-chlorocyclohexanone oxime [**2**, mp 129–130 °C (from diethyl ether)] was obtained in 96% yield: ^{1}H NMR ($CDCl_3$) δ 4.43 (br t, CHCl, 1 H), 3.32 (s, OMe, 3 H), 3.16 (s, OMe, 3 H), 2.16–1.5 (m, $(CH_2)_3$, 6 H); ^{13}C NMR ($CDCl_3$) δ 152.25 (s, C=N), 99.33 (s, $C(OMe)_2$), 59.54 (d, CHCl), 49.55 (q, CH_3O), 47.25 (q, CH_3O), 30.10 (t, CC=N), 21.60 (t, CCCl), 18.93 (t, CCC=N).

Anal. Calcd for $C_8H_{14}NO_2Cl$: C, H, N, O, Cl(17.11). Found: C, H, N, Cl(16.30).

(b) Reaction with Sulfuryl Chloride. To a solution of 2,2-dimethoxycyclohexanone oxime (**1**; 1.73 g, 10 mmol) in 10 mL of dry methylene chloride was added a solution of sulfuryl chloride (1.7 g, 12 mmol) in 10 mL of methylene chloride dropwise over 15 min, maintaining reaction temperature below 32 °C. After being stirred for 1 h at room temperature, the reaction mixture was worked up as above to give **2** in approximately the same yield.

2,2-Dimethoxy-3-chloro-5-*tert*-butylcyclohexanone Oxime. A suspension of 2,2-dimethoxy-5-*tert*-butylcyclohexanone oxime (4.58 g, 20 mmol) in dry methylene chloride was clorinated as above (1.5 g, 21 mmol). There was obtained 4.6 g of 2,2-dimethoxy-3-chloro-5-*tert*-butylcyclohexanone oxime: mp 156–157 °C; 87% yield; ^{1}H NMR ($CDCl_3$) δ 9.63 (br s, NOH, 1 H), 4.43 (br t, CClH, 1 H), 3.3 (s, OMe, 3 H), 3.13 (s, OMe, 3 H), 2.6–1.2 (m, CH_2's, 5 H), 0.9 (s, *t*-Bu, 9 H); ^{13}C NMR ($CDCl_3$) δ 152.96 (s, C=N), 99.38 (s, $C(OMe)_2$), 59.73 (d, CCl), 49.79 (q, OCH_3), 47.63 (q, OCH_3), 40.40 (t, CC=N), 32.30 (s, $C(CH_3)_3$), 31.64 (d, $CC(CH_3)_3$) 27.43 (q, CH_3), 23.12 (t, CCClH). Anal. ($C_{10}H_{22}NO_3Cl$) C, H, N.

2,2-Dimethoxy-3-chlorocyclooctanone Oxime. To a solution of 2,2-dimethoxycyclooctanone oxime (5.02 g, 25 mmol) in dry methylene chloride (50 mL) was added chlorine (1.78 g 25 mmol), and the reaction mixture was worked up as before. There was obtained 5.3 g (90%) of 2,2-dimethoxy-3-chlorocyclooctanone oxime: mp 145–147 °C (diisopropyl ether); ^{1}H NMR ($CDCl_3$) δ 9.67 (br s, NOH, 1 H), 4.43 (t, CHCl), 3.4 (s, OMe), 3.2 (s, OMe), 2.83–1.2 (m, 10 H). Anal. ($C_{10}H_{18}NO_3Cl$): C, H, N.

2,2-Dimethoxy-3-chlorocyclododecanone Oxime. Treatment of 2,2-dimethoxycyclododecanone oxime (6.42 g, 25 mmol) in methylene chloride (50 mL) with chlorine (1.77 g, 25 mmol) in the presence of hydrogen chloride (1 g, 25 mmol), as above, gave about a 50% yield of the crude oxime (NMR), which was not purified further.

3-Oximido-4,4-dimethoxy-5-chloroheptane. 3-Oximido-4,4-dimethoxyheptane (4.72 g, 25 mmol) in dry methylene chloride containing a catalytic quantity of anhydrous hydrogen chloride (0.2 g) was treated with chlorine (1.8 g, 25 mmol) as before. The 3-oximido-4,4-dimethoxy-5-chloroheptane was obtained as an oil: 62% yield; ^{1}H NMR ($CDCl_3$) δ 9.5 (br s, NOH, 1 H), 3.98 (dd, CHCl, 1 H), 3.37 (s, OMe, 3 H), 3.27 (s, OMe, 3 H), 1.8–0.4 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 159.15, 160.95 (2 s, C=N), 103.02 (s, $C(OCH_3)_2$), 65.32, 58.68 (2 d, CCl), 50.28 (q, OCH_3), 48.82 (q, OCH_3), 20.60 (t, CCCl), 16.17 (t, CC=N), 11.83 (CCCCl), 10.15 (q, CCC=N); mass spectrum (CI, methane), *m/e* 224 (MH^+) 206 ($MH^+ - H_2O$), 192 ($MH^+ - CH_3OH$), 188 (MH^+ – HCl), 156 ($MH^+ - CH_3OH$ – HCl). Anal. ($C_{19}H_{18}NO_3Cl$): C, H, N.

2,2-Dimethoxy-3-bromocyclohexanone Oxime. To a solution of 2,2-dimethoxycyclohexanone oxime (**1**; 8.65 g, 50 mmol) in dry methylene chloride (40 mL) was introduced anhydrous hydrogen chloride (2 g, 55 mmol). A solution of bromine (8.5 g, 53 mmol) in 10 mL of methylene chloride was added over 15 min. A workup as above gave 11.8 g (94% yield) of a light tan solid which was crystallized from diisopropyl ether: mp 101–102 °C; ^{1}H NMR ($CDCl_3$) δ 9.67 (br s, NOH, 1 H), 4.53 (t, CHBr, 1 H), 3.3 and 3.17 (2 s, OCH_3, 6 H), 2.4–1.4 (m, CH_2's, 6 H). Anal. ($C_8H_{14}NO_3Br$): C, H, N.

2,2-Dimethoxy-3-bromocyclooctanone Oxime. To a solution of 2,2-dimethoxycyclooctanone oxime (5.02 g, 25 mmol) in 40 mL of methylene chloride was added an excess of hydrogen chloride. A solution of bromine (2 g, 25 mmol) in 10 mL of methylene chloride was then added over 15 min and then the reaction mixture worked up as above. ^{1}H NMR analysis of the crude product indicated about a 50% yield of the 3-bromo derivative.

Reaction of 6-Oximido-1,4-dioxaspiro[4.5]decane with Chlorine. 6-Oximido-1,4-dioxaspiro[4.5]decane (9.9 g, 58 mmol) in 100 mL of dry methylene chloride was treated with a slow stream of chlorine gas (4.1 g, 58 mmol) over a 90-min period. A workup as before gave 12.25 g of light brown liquid. According to ^{1}H NMR the main component in the product mixture was 5-[(2-chloroethoxy)carbonyl]pentanehydroximoyl chloride (**5**): ($CDCl_3$) δ 9.3 (s, NOH, 1 H), 4.33 (t, CH_2Cl, 2 H), 3.67 (t, CH_2O, 2 H), 2.4 (m, CH_2, 4 H), 1.73 (m, CH_2, 4 H). From the presence of the small overlapping triplets at δ 4.33 and 3.67, as well as from the presence of the infrared bands in the IR spectrum at 2300 (C≡N—O) 2220 cm^{-1} (C≡N) and from the mass spectral analysis (follows), it appears that small quantities of 5-[(2-chloroethoxy)carbonyl]pentanenitrile (**6**), 5-(2-hydroxyethoxy)carbonyl]-pentanehydroximoyl chloride (**7**), and 5-[(2-chloroethoxy)-carbonyl]pentanenitrile oxide (**8**) were also present. Mass spectrum (I, methane): for **5** with M at *m/e* 242 (2 Cl), 206 (1 Cl, M – HCl, **8**); for **6** with MH^+ at *m/e* 190 (1 Cl), 154 (MH^+ – HCl), 123 (1 Cl), 110, 63, 62; for **7** with MH^+ at *m/e* 224 (1 Cl), 206 (1 Cl, $MH^+ - H_2O$), 188 (MH^+ – HCl).

5-(Methoxycarbonyl)pentanehydroximoyl Chloride (10). To a solution of 2,2-dimethoxycyclohexanone oxime (**1**; 4.32 g, 25 mmol) in 50 mL of anhydrous methanol were added anhydrous disodium phosphate (11.0 g, 77 mmol) and water (0.5 g, 28 mmol). The mixture was treated with chlorine (1.8 g, 25 mmol) at 25 °C over a 15-minute period. After the mixture was stirred for 30 min, the solids were filtered off, and most of the solvent was removed by evaporation. Methylene chloride (50 mL) was added, the mixture filtered, and the solvent evaporated at room temperature. There was obtained 4.8 g (94% yield) of a red-brown liquid: ^{1}H NMR ($CDCl_3$) δ 9.2 (s, NOH, 1 H), 3.67 (s, OCH_3, 3 H), 2.5 (m, CH_2, 4 H), 1.67 (m, CH_2, 4 H); ^{13}C NMR ($CDCl_3$) δ 1.74.57 (s, COO), 141.04 (s, CCl=N), 51.86 (q, OCH_3), 36.21 (t, CC=O), 33.62 (t, CCl), 25.72 (t, CCCO), 23.80 (t, CCCl).

7-(Methoxycarbonyl)heptanehydroximoyl Chloride (13). With the same quantities of the reagents as above, 2,2-dimethoxycyclooctanone oxime (5.02 g, 25 mmol) was converted to the hydroximoyl chloride **13**: ^{1}H NMR ($CDCl_3$) δ 8.83 (s, NOH, 1 H), 3.7 (s, OCH_3, 3 H), 2.43 (m, CH_2, 4 H), 1.43 (m, CH_2, 8 H); ^{13}C NMR ($CDCl_3$) δ 174.84 (s, C=O), 144.09 (s, CClN=), 51.68 (q, OCH_3), 36.40 (t, CC=O), 33.98 (t, CCCl), 28.66 (t, CCCCO), 28.07 (t, CCCCl), 26.08 (t, CCC=O), 24.73 (t, CCCCl).

5-(Methoxycarbonyl)valeronitrile Oxide (9) and 4,5-Bis-[4-(methoxycarbonyl)butyl]furoxan (11). A reaction mixture of 2,2-dimethoxycyclohexanone oxime (**1**; 8.65 g, 50 mmol), sodium bicarbonate (12.6 g, 150 mmol), methylene chloride (25 mL), and water (25 mL) was stirred in an ice–water bath. Chlorine (3.5 g, 50 mmol) was introduced over 30 min, and the mixture was then stirred for 1.5 h. The methylene chloride layer was separated, dried, and evaporated at room temperature. There was obtained 7.2 g (92% yield) of a yellow liquid which according to IR analysis was a mixture of the nitrile oxide **9** (2300 cm^{-1}) and furoxan **11** (1603 cm^{-1}). When the mixture was allowed to stand overnight at room temperature, the infrared band at 2300 cm^{-1} disappeared, and the band at 1603 cm^{-1} strengthened, indicating dimerization of the nitrile oxide **9** into furoxan **11**. Column chromatography on neutral alumina gave **11**: ^{1}H NMR ($CDCl_3$) δ 3.67 (s, OCH_3, 6 H), 2.37 (m, CH_2, 8 H), 1.7 (m, CH_2, 8 H); ^{13}C NMR ($CDCl_3$) δ 173.48 (s, COO), 157.39 (s, C=N(O)O), 115.47 (s, C=N—O), 51.61 (q, OCH_3), 33.38 (t, CC=N(O)O); CI mass spectrum (methane), *m/e* 315 (MH^+), 294 (MH^+ – O), 283 (MH^+ – MeOH); CI mass spectrum (ammonia), *m/e* 315 (MH^+), 299 (MH^+ – O), 283 (MH^+ – MeOH).

5-[ω-(Methoxycarbonyl)butyl]-1,3,2,4-dioxathiazole *S*-Oxide[11] (14). Addition of bromine (2 g, 25 mmol) to a well-stirred mixture of 2,2-dimethoxycyclohexanone oxime (**1**; 4.32 g, 25 mmol), disodium phosphate (10.65 g, 75 mmol) in 40 mL of methylene chloride, and 40 mL of water at room temperature, followed by separation of methylene chloride layer and drying, gave crude nitrile oxide **9** in solution. Without isolation, sulfur dioxide (1.8 g, 28 mmol) was introduced, the mixture stirred for 15 min, and the solvent evaporated. There was obtained 5.0 g (90% yield) of **14** as a slightly tan liquid: ^{1}H NMR ($CDCl_3$) δ 3.67 (s, OCH_3,

3 H), 2.7 (m, CH_2C=N, 2 H), 2.37 (m, CH_2C—O, 2 H), 1.73 (m, CH_2, 4 H); ^{13}C NMR ($CDCl_3$) δ 1.73.34 (s, C=O), 158.81 (s, C=N), 51.48 (q, OCH_3), 33.22 (t, CC=O), 24.76 (t, CC—N), 23.92 (t, CCC—O), 23.10 (t, CCC—N).

The same product was also obtained from the reaction of 4-(methoxycarbonyl)pentanehydroximoyl chloride (**10**) with 1 molar equiv of pyridine and sulfur dioxide in methylene chloride solution.

5-[ω-(Methoxycarbonyl)hexyl]-1,3,2,4-dioxathiazole *S*-Oxide[11] (15). Similarly 2,2-dimethoxycyclooctanone oxime (5.02 g, 25 mmol) was converted to the sulfur dioxide complex **15**: 4.5 g (72.6% yield). ^1H NMR ($CDCl_3$) δ 3.67 (s, OCH_3, 3 H), 2.67 (m, CH_2C=N, 2 H), 2.33 (m, CH_2C=O, 2 H), 1.47 (m, CH_2, 8 H); ^{13}C NMR ($CDCl_3$) δ 173.87 (s, C=O), 159.17 (s, C=N), 51.37 (q, OCH_3), 33.80 (t, CC=O), 28.38 (t, CCCCC=N), 25.14 (t, CCC=O), 24.62 (t, CC—N), 23.23 (t, CCC=N).

Methyl 5-Isocyanatovalerate (16). The sulfur dioxide complex of 5-(methoxycarbonyl)pentanenitrile oxide (**14**) was refluxed in cyclohexane until sulfur dioxide evolution ceased.[11] Evaporation of the cyclohexane gave about a 60% yield of methyl 5-isocyanatovalerate (**16**): bp 50 °C (0.4 mm); ^1H NMR ($CDCl_3$) δ 3.67 (s, OCH_3, 3 H), 3.33 (m, CH_2N, 2 H), 2.37 (m, CH_2CO, 2 H), 1.67 (m, CH_2, 4 H). A small sample of the isocyanate was treated with aniline to give the *N*-phenyl-*N'*-[(4-methoxycarbonyl)butyl]urea: mp 106–108 °C (ethyl acetate); ^{13}C NMR ($CDCl_3$) δ 173.91 (s, C=O), 156.85 (s, NCN), 139.19 (s, N—$C(CH_2)_5$), 51.49 (q, OCH_3), 39.69 (t, CN), 33.56 (t, CC=O), 29.60 (t, CCN), 22.13 (t, CCC=O). Anal. ($C_{13}H_{18}N_2O_3$): C, H, N.

Methyl 7-isocyanatoheptanoate (17) was prepared in a manner similar to that above: ^1H NMR ($CDCl_3$) δ 3.67 (s, OCH_3, 3 H), 3.33 (m, CH_2N, 2 H), 2.33 (m, CH_2C=O, 2 H), 1.43 (m, CH_2, 8 H); ^{13}C NMR ($CDCl_3$) δ 173.87 (s, C=O), 122.6 (s, NCO), 51.36 (q, OCH_3), 43.12 (t, CN) 33.91 (t, CC=O), 31.34 (t, CCN), 28.63 (t, CCCC=O), 26.42 (t, CCCN), 24.98 (t, CCC=O).

Reaction of 2,2-Dimethoxycyclohexanone oxime (1) with Chlorine in the Presence of Pyridine. A solution of 2,2-dimethoxycyclohexanone oxime (**1**; 8.65 g, 50 mmol) in dry methylene chloride (50 mL) and pyridine (3.95 g, 50 mmol) was treated with chlorine (3.55 g, 50 mmol) over 1.2 h at 15 °C. After being stirred for 2 h at room temperature, the solution was washed three times with equal volumes of cold water and evaporated. There was obtained 9.8 g of yellow liquid which, according to the mass spectrum was a mixture of 5-(methoxycarbonyl)valeronitrile, 5-methoxycarbonyl)valeronitrile oxide (**9**), 4-methoxycarbonyl)-pentanehydroximoyl chloride (**10**), 4,5-bis[4-(methoxycarbonyl)butyl]furoxan (**11**), and the corresponding furazan.

2-Chloro-5-(methoxycarbonyl)valeronitrile (18). To a solution of 2,2-dimethoxy-3-chlorocyclohexanone oxime (**2**; 1 g, 4.8 mmol) in 10 mL of dry methylene chloride was added a solution of ethyldimethoxycarbonium tetrafluoroborate (0.5 mmol) in 2 mL of the same solvent dropwise at room temperature, causing an exothermic reaction. After being stirred for 30 min, the reaction mixture was worked up to give methyl 2-chloro-5-cyanovalerate (**18**).

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Registry No. **1**, 52540-36-0; **2**, 58700-10-0; **3**, 52841-56-2; **4**, 58158-90-0; **5**, 81617-18-7; **6**, 81617-19-8; **7**, 81617-20-1; **8**, 81617-21-2; **9**, 81617-22-3; **10**, 81617-23-4; **11**, 81617-24-5; **12**, 64950-92-1; **13**, 81617-25-6; **14**, 81617-26-7; **15**, 81617-27-8; **16**, 70288-68-5; **17**, 64054-33-7; **18**, 58700-11-1; 2,2-dimethoxy-5-*tert*-butylcyclohexanone oxime, 68226-32-4; 2,2-dimethoxy-3-chloro-5-*tert*-butylcyclohexanone oxime, 70165-53-6; 2,2-dimethoxy-3-chlorocyclooctanone oxime, 70165-52-5; 2,2-dimethoxy-3-chlorocyclododecanone oxime, 81617-28-9; 2,2-dimethoxycyclododecanone oxime, 68226-33-5; 3-oximido-4,4-dimethoxy-5-chloroheptane, 70165-56-9; 3-oximido-4,4-dimethoxyheptane, 68226-61-9; 2,2-dimethoxy-3-bromocyclohexane oxime, 70165-54-7; 2,2-dimethoxy-3-bromocyclooctanone oxime, 70165-55-8; 5-methoxycarbonylvaleronitrile, 3009-88-9.

Substitutions on Pyridines Activated by Oxazolines via Nucleophilic Additions or Metalation–Alkylation

A. I. Meyers* and Richard A. Gabel

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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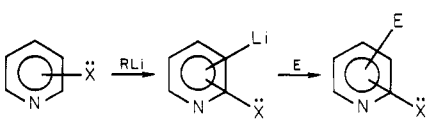
Pyridyloxazolines, derived from nicotinic acid or isonicotinic acid, have been shown to metalate at the 4- and 3-positions, respectively. These react with a variety of electrophiles to provide 4- and 3-substituted pyridines in good yield. Alternatively, 3-pyridyloxazolines, when treated with organolithium or Grignard reagents, give addition to the 4-position and provide a series of 4-substituted 1,4-dihydropyridines.

Substitution on the pyridine ring has long been an important synthetic goal, and a variety of methods have been described, the most prominent of which is halogen–metal exchange on bromopyridines.[1] The direct metalation of pyridines has, until recently, been precluded from the arsenal of substitution methods mainly because most strong bases act as nucleophiles and add across the C=N link.[2] However, in the last few years a number of elegant techniques[3] have been reported which allow direct removal

Scheme I



X = CO_2Et, $CONR_2$

of a ring proton by organolithium bases, provided an adjacent electron withdrawing group, also capable of lithium

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