(*E*)-1-Phenyl-2-tosylethene (12). The title compound was obtained in 87% yield (3.78 g) from dehydroiodination of 6.6 g of **1**; mp 120–121 °C (ethanol; lit.[9] mp 120–121 °C).

(*E*)-1-Tosylhexene (13). Dehydroiodination of 18.3 g of **2** afforded 10.7 g (90%) of **13**: bp 148–153 °C (0.1 torr); IR (neat) 1650 (C=C), 1300 (SO_2, asym), 1140 (SO_2, sym) cm^{-1}; NMR (CCl_4) 0.9 (t, 3 H, CH_3), 1–1.7 (m, 4 H, $(CH_2)_2$), 2.2 (q, 2 H, $=CH_2$, J_{bc} = 6 Hz), 6.3 (dt, 1 H, $=CH_aC(H_c)_2$, J_{ab} = 15 Hz, J_{ac} = 2 Hz), 6.8 (td, 1 H, $=CH_bTs$, J_{ab} = 15 Hz, J_{bc} = 6 Hz), 7.3 (d, 2 H, *m*-H), 7.7 (d, 2 H, *o*-H, J_{om} = 8 Hz).

1-Tosylcyclopentene (14). Dehydroiodination of 5.25 g of 1-iodo-2-tosylcyclopentane (**3**) with 2.5 equiv of triethylamine gave 2.69 g (81%) of **14**, mp 115–116 °C (ethanol; lit.[24] mp 115–116 °C).

2-Tosyl-3-methyl-3-butene (15). Dehydroiodination of 22.75 g of **4** gave 12.3 g (85%) of **15**: mp 66–67 °C (ethanol); IR (KBr) 1650 (C=C), 1300 (SO_2, asym), 1100 (SO_2, sym) cm^{-1}; NMR ($CDCl_3$) δ 1.88 (s, 3 H, CH_3, H_a), 2 (q, 3 H, CH_3, H_c), 2.2 (q, 3 H, CH_3, H_b, J_{bc} = 1.2 Hz), 2.45 (s, 3 H, $CH_3C_6H_4$), 7.37 (d, 2 H, *m*-H), 7.8 (d, 2 H, *o*-H, J_{om} = 7.5 Hz).

1-Tosylcyclohexene (16). The title compound could be obtained from dehydroiodination of either *trans*- or *cis*-1-iodo-2-tosylcyclohexane with triethylamine. The yields were 76% (3.32 g from 6.14 g of **5**) and 77% (99 mg from 196 mg of **6**), respectively, mp 81–82 °C (ethanol; lit.[24] mp 82–83 °C).

1-(Phenylsulfonyl)cyclohexene (17). Dehydroiodination of either **7** (7.7 g) or **8** (379 mg) with triethylamine gave **17** in 83% (4.02 g) or 89% (223 mg) yield, respectively. But the cis isomer **8** reacted much faster than the trans isomer **7**. Recrystallization from ethanol gave pure **17**: mp 40–42 °C; IR (KBr) 1620 (C=C), 1300 (SO_2, asym), 1140 (SO_2, sym) cm^{-1}; NMR ($CDCl_3$) δ 1.65 (m, 4 H, $(CH_2)_2$), 2.3 (t, 4 H, $=C(CH_3)CH_2$), 7.1 (q, 1 H, $=CHCH_3$, J = 2 Hz), 7.7 (m, 5 H, C_6H_5).

1-Iodo-2-(methanesulfonyl)-1-phenylethane (18). Reaction of 2.08 g of styrene (0.02 mol) and 4.12 g (0.02 mol) of methanesulfonyl iodide at 20–25 °C gave 5.62 g (57.2%) of **18**: mp 104–106 °C (3:1 $CHCl_3$:hexane); IR (KBr) 1280 (SO_2, asym), 1120 (SO_2, sym) cm^{-1}; NMR ($CDCl_3$) δ 2.3 (s, 3 H, CH_3SO_2), 4.2 (2 d, 2 H, CH_2SO_2, J = 11 and 6 Hz), 5.45 (dd, 1 H, CHI, J = 11.6 Hz), 7.2 (m, 5 H, C_6H_5).

Anal. Calcd for $C_9H_{11}SO_2I$: C, 34.84; H, 3.55; S, 10.35; I, 40.94. Found: C, 35.11; H, 3.74; S, 10.36; I, 41.06.

1-(*n*-Butanesulfonyl)-2-iodohexane (19). Reaction of 1.68 g of 1-hexene (0.02 mol) and 4.96 g (0.02 mol) of *n*-butanesulfonyl iodide at 20–25 °C gave 5.65 g (85.1%) of **19**. The product was first purified by chromatography on a silica gel column in the dark using benzene as eluent, followed by recrystallization from 3:1 methanol:*n*-hexane to give white crystals of **19**: mp 35–36 °C; IR (neat) 1290 (SO_2, asym), 1100 (SO_2, sym) cm^{-1}; NMR ($CDCl_3$) δ 1 (t, 6 H, CH_3), 1.2–2.2 (m, 10 H, $(CH_2)_3$), 3.15 (2 d, 2 H, CH_2CHI, J = 6 Hz), 3.75 (2 d, 2 H, SO_2CH_2CI, J = 6 and 1 Hz), 4.7 (m, 1 H, CHI).

Anal. Calcd for $C_{10}H_{21}SO_2I$: C, 36.14; H, 6.33; S, 9.64; I, 38.22. Found: C, 36.29; H, 6.08; S, 10.03; I, 37.97.

1-Iodo-2-(*n*-butanesulfonyl)cyclopentane (20). Reaction of equimolar amounts (0.02 mol) of *n*-butanesulfonyl iodide (4.96 g) and cyclopentene (1.36 g) at 30–35 °C gave 3.2 g (50.6%) of **20**. Purification on a silica gel column in the dark with benzene as eluent gave an analytical pure sample: mp 12–13 °C; IR (neat) 1300 (SO_2, asym), 1130 (SO_2, sym) cm^{-1}; NMR ($CDCl_3$) δ 0.95 (t, 3 H, CH_3), 1.1–2.9 (m, 10 H, $(CH_2)_2$ and ring protons), 3 (2 d, 2 H, CH_2SO_2, J = 6 Hz), 3.8 (m, 1 H, $CHSO_2$), 4.7 (m, 1 H, CHI).

Anal. Calcd for $C_9H_{17}SO_2I$: C, 34.29; H, 5.40; S, 11.69; I, 40.29. Found: C, 34.57; H, 5.48; S, 11.76; I, 40.03.

2-Iodo-2-methyl-3-(methanesulfonyl)butane (21). Reaction of equimolar amounts (0.02 mol) of methanesulfonyl iodide (4.12 g) and 2-methyl-2-butene (1.4 g) at 0 °C gave 2.8 g (50.9%) of the title compound. Purification on a silica gel column in the dark with benzene as eluent gave 1.8 g (33%) of pure **21**: IR (neat) 1300 (SO_2, asym), 1180 (SO_2, sym) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (d, 3 H, CH_3CH, J = 6 Hz), 2.0 (s, 3 H, CH_3CI), 2.12 (s, 3 H, CH_3CI), 3.72 (s, 3 H, CH_3SO_2), 4.53 (q, 1 H, $CHSO_2$, J = 6 Hz).

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Registry No. 1, 19523-30-9; 2, 71963-96-7; 3, 71963-97-8; 4, 71963-98-9; 5, 71963-99-0; 6, 71964-00-6; 7, 71974-93-1; 8, 71964-01-7; 9, 71964-02-8; 10, 71964-03-9; 11, 71964-04-0; 12, 16212-08-1; 13, 71964-05-1; 14, 67963-04-6; 15, 71964-06-2; 16, 67963-03-5; 17, 59059-70-0; 18, 71964-07-3; 19, 71964-08-4; 20, 71964-09-5; 21, 71964-10-8; styrene, 100-42-5; 1-hexene, 592-41-6; cyclopentene, 142-29-0; 2-methyl-2-butene, 513-35-9; cyclohexene, 110-83-8; 1-methylcyclohexene, 591-49-1; 1-phenylcyclohexene, 771-98-2; tosyl iodide, 1950-78-3; benzenesulfonyl iodide, 98-09-9; methanesulfonyl iodide, 42790-82-9; butanesulfonyl iodide, 71964-11-9; butanesulfonyl chloride, 2386-60-9; cupric chloride, 7447-39-4; sodium *p*-toluenesulfinite, 824-79-3; sodium benzenesulfinite, 873-55-2; sodium methylsulfinite, 20277-69-4; sodium butylsulfinite, 16642-95-8.

(24) F. G. Bordwell and R. J. Kern, *J. Am. Chem. Soc.*, 77, 1141 (1955).

Titanium Trichloride Reduction of Substituted *N*-Hydroxy-2-azetidinones and Other Hydroxamic Acids

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A mild method of reduction of the N–O bond of substituted *N*-hydroxy-2-azetidinones was required to complete a hydroxamic acid mediated synthesis of substituted β-lactams. Of the several reduction methods studied, most either failed to reduce the N–O bond, cleaved the 2-azetidinone ring, or were inefficient and inconvenient. However, buffered titanium trichloride cleanly reduced the N–O bond of the *N*-hydroxy-2-azetidinones under conditions compatible with a peripheral acid-sensitive *tert*-butoxycarbonyl (Boc) group and the base-sensitive chiral center at C_3. These results therefore constitute an efficient synthesis of β-lactams from substituted serinehydroxamic acids. The competitive C–O and N–O reductions of noncyclic hydroxamic acids of various substitution patterns are also described.

During the development of a synthesis of β-lactams from hydroxamic acids,[1] we required a mild method of reduction of the N–O bond of substituted *N*-hydroxy-2-azetidinones (eq 1). A number of efficient methods of N–O reduction

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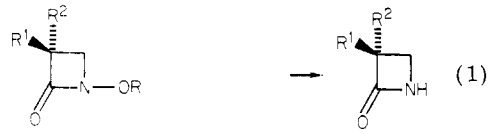


1 2 (1)

3, R = CH_2Ph, $R^1 = CH_3$, $R^2 = CH_3$
4, R = CH_3, $R^1 = CH_3$, $R^2 = CH_3$
5, R = H, $R^1 = CH_3$, $R^2 = CH_3$
6, R = CH_2Ph, R^1 = BocNH, R^2 = H
7, R = CH_3, R^1 = BocNH, R^2 = H

have been described. However, when several of these methods were applied to the desired reduction, either no reaction or undesired ring opening occurred (Table I). The one successful reduction with Raney nickel was made inconvenient by the required preparation and immediate use of very active (w-6) catalyst, long reaction times, and low (22%) yield in the case of the 3-BocNH-substituted derivative **6**. Consequently, another method was sought. We describe here the efficient N–O reduction of *N*-hydroxy-2-azetidinones with titanium trichloride and the unusual results obtained with other hydroxamic acids.

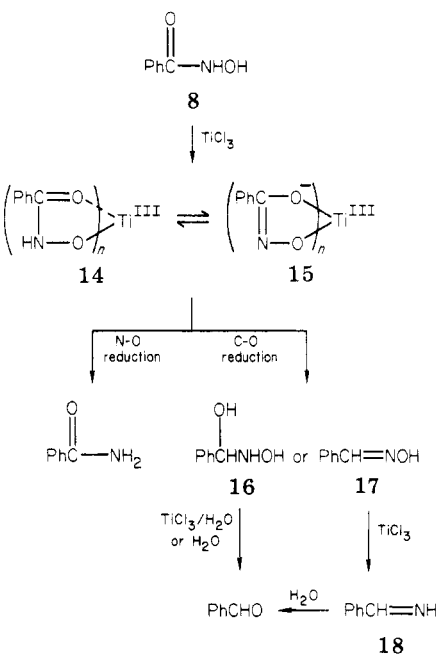
Titanium trichloride has been used to reduce the N–O bonds of nitro compounds,[2,3] oximes,[4] and heterocyclic *N*-oxides[5] but not hydroxamic acids, although titanium(IV) complexes of hydroxamic acids are known.[6] Therefore, several model compounds were prepared in order to test the applicability of titanium trichloride to the N–O reduction of hydroxamic acids and *N*-hydroxy-2-azetidinones. The results are summarized in Tables II and III.

Results and Discussion

Dropwise addition of 100 mol % (1 equiv) of a 20% solution of $TiCl_3$ in water to a sodium acetate buffered solution of benzohydroxamic acid (**8**) in methanol–water under a nitrogen atmosphere resulted in immediate discharge of the dark blue color of titanium(III) and formation of a yellow suspension. Addition of another 100 mol % of $TiCl_3$ required to complete the reduction gave a dark blue suspension. Extractive workup yielded benzamide as expected and, surprisingly, benzaldehyde in 26% relative yield (Table II). A control experiment indicated that benzamide was not reduced under the same conditions. Thus a mechanism which allows competitive C–O or C–N reduction as well as the desired NO reduction was apparently operating.

On the basis of the known ability of hydroxamic acids to chelate many metal atoms,[7] competitive C–O reduction appeared more reasonable (Scheme I). By analogy to titanium(IV), ferric ion, and other metal complexes,[8] formation of the titanium(III) complex **14** should elongate and weaken the carbonyl bond of the hydroxamic acid and thereby promote less selective reduction by the titanium

Scheme I



(i.e., competitive C–O as well as N–O reduction). Subsequent formation of **16** or **17** would result in eventual aldehyde formation. Simple hydrolysis of **16** would yield benzaldehyde whereas conversion of the oxime **17** to the aldehyde would first require further reduction to the imine **18** followed by hydrolysis. As already indicated, the $TiCl_3$-mediated conversion of oximes to the parent carbonyl compounds is well-known.[2-4]

Since the ligand-to-metal ratio of other metal complexes of hydroxamic acids is pH dependent,[10] performing the reduction in the absence of a buffer (pH 1–2) was anticipated to decrease the ligand-to-metal ratio and perhaps affect the amount of aldehyde produced. Indeed, such a reaction gave only trace amounts of aldehyde (Table II, entry 3). As expected, a change from acetate to the more basic buffer Na_2CO_3 resulted in similar amounts of aldehyde produced. By analogy to methods of isolation of titanium(IV) hydroxamate complexes,[6] an attempt to isolate a titanium(III) complex by extraction with *n*-amyl alcohol after addition of only 50 mol % of $TiCl_3$ gave only a light yellow solution (λ_{max} 322 nm) which could not be further characterized.

To further test the scope of this reduction, we prepared and studied simple hydroxamic acids of all the various substitution patterns. Table II provides structures for the compounds studied (**9**–**13**) as well as the results of the reduction. *N*-Alkyl-substituted hydroxamic acids such as **9** were reduced to the amide with little or no aldehyde production. In this case formation of the complex analogous to **15** would require the nitrogen to bear a positive charge. *O*-Alkyl-substituted hydroxamic acids (i.e., **10**) also were reduced to the amide with formation of intermediate amounts of aldehyde. Since the pK values of *O*-alkylhydroxamic acids and *N*-alkylhydroxamic acids (i.e., **9**) are essentially the same (pK = 8–10),[11] at first consideration, they might be anticipated to serve equally well as ligands, and the corresponding pairs of structures **19** and **20** (eq 2) or **21** and **22** (eq 3) might explain the competitive C–O vs. N–O reduction. However, both Ti^{3+} and Fe^{3+} are

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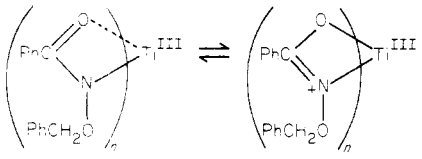
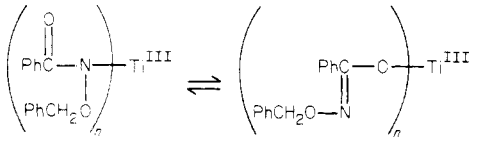
(9) The ligand-to-metal ratio (i.e., value of *n*) was not determined, but under neutral conditions the value of *n* most probably is 3.[10]
(10) Epstein, L. M.; Straub, D. K. *Inorg. Chem.* **1969**, *8*, 453–7.
(11) Exner, O.; Simon, W. *Collect. Czech. Chem. Commun.* **1965**, *30*, 4078.



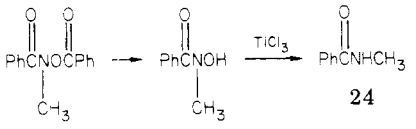
19 20 (2)



21 22 (3)

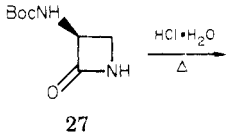
preferentially hexacoordinate with octahedral geometry.[12] Preparation of models suggests that four-membered ring complexes such as **19** and **20** are unlikely. In fact, **10** does not give a positive ferric chloride color test characteristic of O-unsubstituted hydroxamic acids.

N,O-Dialkylhydroxamic acids **13** and **3** were not reduced, thereby recomfirming the need for an acidic chelation site. However, the *N*-alkyl-*O*-acylhydroxamic acid **12** did reduce to the amide and a trace of aldehyde. A control reaction indicated that, under the same conditions but in the absence of $TiCl_3$, hydrolysis of **12** occurs to give the O-unsubstituted hydroxamic acid **23**. Subsequent addition of $TiCl_3$ resulted in reduction primarily to **24** (eq 4).



12 23 24 (4)

Depression of aldehyde formation upon N-substitution and the observation that *N*-hydroxy-2-azetidinones (i.e., **5**) do not give a positive ferric chloride test[13] indicated that competitive C–O reduction would be minimized during the $TiCl_3$-mediated N–O reduction of the *N*-hydroxy-2-azetidinones to the 2-azetidinones required for our β-lactam syntheses. In fact, $TiCl_3$ reduction of the *N*-hydroxy-2-azetidinones proceeded efficiently (Table III) with no aldehyde isolable in any instance. The reduction of **26** indicates that buffered $TiCl_3$ is compatible with a base-sensitive chiral position and the acid-sensitive *tert*-butoxycarbonyl (Boc) protecting group. Structure and retention of chirality in this case were also confirmed by hydrolysis of the product β-lactam **27** (eq 5). The resulting



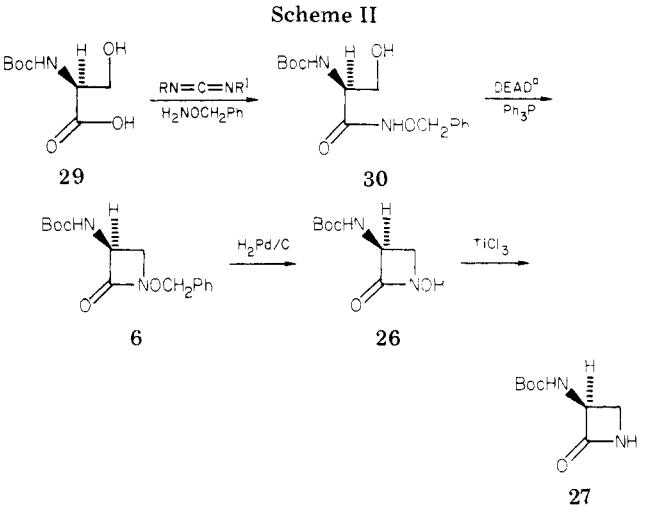
27 L-$H_2NCH_2CH(NH_2)CO_2H$ (5)

28 ($[\alpha]_D$ +22.5° (lit.[15] $[\alpha]_D$ +25°))

L-2,3-diaminopropionic acid (**28**) was identical with an authentic sample by melting point, mixture melting point, amino acid analysis, and comparison of optical rotation.[14]

Thus this facile $TiCl_3$-mediated reduction of the N–O bond of **26**, coupled with the previously described preparation of **26**,[1] provides an efficient synthesis of optically active substituted 3-amino-2-azetidinones of interest for the synthesis of β-lactam antibiotics (Scheme II).

Scheme II



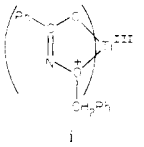
[a] DEAD = diethyl azodicarboxylate.

Experimental Section

General Comments. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. NMR spectra were determined in chloroform-*d* with tetramethylsilane as a reference by using a Varian A-60A spectrometer. Mass spectra were recorded on an AEI Scientific Apparatus MS 902 or Du Pont DP 102 spectrometer. Elemental analyses were performed by Midwest Microlabs. Gas chromatographic analyses were performed on a Varian Aerograph Model 940. THF was distilled from $LiAlH_4$ directly before use. Amino acid analysis of DAPA (**28**) was performed on a Beckman 116 analyzer.

Reduction of Benzohydroxamic Acid (8). Benzohydroxamic acid[17] (**8**; 274 mg, 2 mmol) was dissolved in 10 mL of methanol. Water (7 mL) and sodium acetate (2 g) were added, and the mixture was stirred magnetically under nitrogen while 3.1 mL of a 20% $TiCl_3$ solution in water (MCB) was added dropwise. During the first half of the addition the dark blue color of the Ti^{3+} was immediately discharged, and a light yellow suspension formed. Upon completion of the addition the blue color persisted. After 1 h the suspension was poured into 30 mL of water and then extracted with three 25-mL portions of ethyl acetate. The combined ethyl acetate was extracted with two 20-mL portions of 5% sodium carbonate to remove acetic acid. After being washed with brine, dried over magnesium sulfate, filtered, and concentrated to 10 mL, the ethyl acetate layer was analyzed directly by gas chromatography which indicated the formation of benzamide and benzaldehyde in 74 and 26% yields, respectively (peaks were identified by coinjection with authentic materials). Removal of the remaining solvent gave 230 mg of an oily solid which gave a positive aldehyde test with 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole.[16] Recrystallization from ethyl acetate–hexanes gave

(12) Cotton, F. A.; Wilkinson, G. "Advanced Inorganic Chemistry", 3rd ed.; Interscience: New York, 1972; p 808. A referee has pointed out structure i is an alternative to **19**–**22**.



i

(13) The lack of a positive ferric chloride test for **5** is presumably due to the inability of a hydroxamic acid constrained to a four-membered ring to fulfill the optimal octahedral geometrical requirements of the ferric ion.

(14) The 10% difference in the optical rotation of **28** from authentic L-DAPA·HCl[15] may be due to partial racemization during hydrolysis. DAPA·HCl obtained from hydrolysis of nocardicin A had $[\alpha]^{20}_D$ +20.3 (1 N HCl): Hashimoto, M.; Komori, T.-A.; Kamiya, T. *J. Am. Chem. Soc.* **1976**, *98*, 3023–5.

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Table I. Reduction of Substituted *N*-Hydroxy-2-azetidinones (1)[a]

no.	R	R^1	R^2	conditions	products (yield, %)
3	CH_2Ph	CH_3	CH_3	H_2, Pd/C, CH_3OH	5 (100)[b]
4	CH_3	CH_3	CH_3		NR
5	H	CH_3	CH_3		NR
3	CH_2Ph	CH_3	CH_3	NaHg, Na_2HPO_4, C_2H_5OH	$C_2H_5O_2CCR^1R^2CH_2NHOR$ (11) + 1 (7.8)
3	CH_2Ph	CH_3	CH_3	Zn, CH_3CO_2H	$HO_2CCR^1R^2CH_2N(COCH_3)OR$ (58)
3	CH_2Ph	CH_3	CH_3	$NaBH_4$, CH_3OH	$HOCH_2CR^1R^2CH_2NHOR$ (22) + 1 (60)
				$LiBH_4$, CH_3OH	$HOCH_2CR^1R^2CH_2NHOR$ (73)
3	CH_2Ph	CH_3	CH_3	$Na_2S_2O_4$, CH_3OH/H_2O	NR
5	H	CH_3	CH_3		NR
31	CH_2Ph	CBz	H	$Na_2S_2O_4$, 6 N HCl, reflux	L-$HO_2CCH(NH_2)CH_2NH_2$ (30)[d] + NH_3 (170)[c] + CH_3COCO_2H
3	CH_2Ph	CH_3	CH_3	H_2, w-6 RaNi, CH_3OH, 72 h	2 (100)
6	CH_2Ph	BocNH[c]	H		2 (27, 22) + 6 (49)
7	CH_3	BocNH	H		2 (27, 50) + 7 (49)

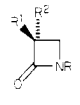
[a] Satisfactory analyses and/or spectroscopic data were obtained for all new compounds (see the Experimental Section). [b] In one trial further reduction gave **2**, not described in the Experimental Section, in 16% yield. This result could not be reproduced. [c] Boc = *tert*-butoxycarbonyl. [d] Relative yields obtained from amino acid analyses.

Table II. Reaction of Hydroxamic Acids ($RC(O)NR^1OR^2$)[a] with $TiCl_3$

no.	R	R^1	R^2	conditions	products (yield, %)
8	Ph	H	H	0.1 M **8**, 0.2 M $TiCl_3$, 1.25 M NaOAc, CH_3OH/H_2O (1:1), 0.5-1 h	$PhC(O)NH_2$ (74), PhCHO (26)[b]
8	Ph	H	H	as above, buffered with 2 M Na_2CO_3	$PhC(O)NH_2$ (85), PhCHO (15)[b]
8	Ph	H	H	as above, no buffer, 1 h	$PhC(O)NH_2$ (83),[c] PhCHO (<0.5)[d]
9	CH_2Ph	CH_3	H	0.1 M **9**, 0.2 M $TiCl_3$, 1.25 M NaOAc, CH_3OH/H_2O (1:1), 2 h	$PhCH_2C(O)NHCH_3$ (64),[c] $PhCH_2CHO$ (<0.5)[d]
10	Ph	H	CH_2Ph	0.1 M **10**, 0.2 M $TiCl_3$, 1.25 M NaOAc, CH_3OH/H_2O (1:1), 3 h	$PhC(O)NH_2$ (91),[c] PhCHO (7),[b] $PhCH_2OH$ (81)[b]
11	Ph	H	COPh	0.02 M **11**, 0.04 M $TiCl_3$, 0.24 M Na_2CO_3, 0.5 h	$PhC(O)NH_2$ (91),[c] PhCHO (4),[b] $PhCO_2H$ (94)[c]
12	Ph	CH_3	COPh	0.1 M **12**, 0.2 M $TiCl_3$, 2.5 M NH_4HCO_3, 2 M Na_2CO_3, CH_3OH/H_2O (1:1), 3 h	$PhC(O)NHCH_3$ (88),[c] PhCHO (1-5),[b,c] $PhCO_2H$ (100)[c]
13	CH_2Ph	CH_3	CH_2Ph	0.1 M **13**, 0.2 M $TiCl_3$, 2.5 M NH_4HCO_3, 2 M Na_2CO_3, CH_3OH/H_2O (1:1), 6.5 h	NR

[a] See the Experimental Section for preparation of the hydroxamic acids. [b] Relative yields determined by GC and/or high-pressure LC. [c] Yields of isolated, purified material. [d] Not isolated or detected by GC; however, a positive test was obtained with the sensitive, aldehyde-specific reagent 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole.[15]

Table III. Reaction of Substituted *N*-Hydroxy-2-azetidinones with $TiCl_3$



compd	R	R^1	R^2	products	yield, %
5	OH	CH_3	CH_3	**25** (5, R = H)	79
3	OCH_2Ph	CH_3	CH_3	NR	
26	OH	BocNH	H	27	67

benzamide: mp 127–128.5 °C; mmp (with authentic benzamide) 127–129 °C.

Repetition of the above reaction with sodium carbonate instead of sodium acetate gave benzamide and benzaldehyde in 85 and 15% relative yields. In the absence of a buffer, benzamide was isolated in 83% yield, and no benzaldehyde could be detected by GC. However, a faint positive test for aldehyde was obtained with 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole.[16]

***N*-Methylphenylacetohydroxamic acid (9)** was prepared in 61% yield from ethyl phenylacetate and *N*-methylhydroxylamine by the method of Hauser and Renfrow:[18] NMR ($CDCl_3$) δ 3.0 (3 H, s), 3.56 (2 H, s), 7.17 (s, 5 H), 9.1 (br s, OH); mass spectrum (CI with CH_4) *m/e* 166 (M + 1); dark red color obtained with 1% $FeCl_3$. $TiCl_3$ reduction (0.1 M **9**, 0.2 M $TiCl_3$, 1.25 M NaO_2CCH_3, CH_3OH–H_2O (1:1), 2 h) gave *N*-methylphenylacetamide in 64% isolated yield after extractive workup; mp 56–57 °C (lit.[19] mp 58 °C).

***O*-Benzylbenzohydroxamic acid (10)**[20] was reduced with $TiCl_3$ by using the same conditions as for the reduction of **9** except the reaction was allowed to proceed for 3 h. Benzamide was isolated in 91% yield (mp 128–129 °C). Benzaldehyde was detected by GC in 7% yield and benzyl alcohol in 81% yield relative to the benzamide.

Reduction of *O*-benzoylbenzohydroxamic acid (11), mp 160.5–162 °C (lit.[18] mp 161–612 °C), was performed at a 0.02 M concentration in methanol–water (1:1) with 0.04 M $TiCl_3$ and 0.24 M Na_2CO_3 for 5 h under N_2 to give benzamide in 91% isolated yield, benzoic acid in 94% isolated yield, and benzaldehyde in 4% GC yield relative to the benzamide.

***N*-Methyl-*O*-benzoylbenzohydroxamic Acid (12).** *N*-Methylhydroxylamine hydrochloride (835 mg, 10 mmol, Aldrich) was dissolved in 30 mL of pyridine. Benzoyl chloride (2.32 mL, 20 mmol) was added. The reaction was exothermic, and a precipitate began to form immediately. After 4 h the reaction mixture was poured into 50 mL of ethyl acetate and then washed with five 20-mL portions of H_2O, three 20-mL portions of 0.05 N NaOH, three 20-mL portions of 0.06 N HCl, and 25 mL of brine. Filtration and evaporation gave an oil which resisted crystallization (lit.[21] mp 58 °C): TLC [silica gel, ethyl acetate–hexanes (1:1)]

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R_f 0.55; NMR ($CDCl_3$) δ 3.55 (s, 3 H), 7.25–8.1 (m, 10 H); mass spectrum (CI with CH_4) m/e 256 (M + 1).

Reduction of **12** (0.1 M) with $TiCl_3$ (0.2 M) in CH_3OH–H_2O (1:1) containing NH_4HCO_3 (2.5 M) and Na_2CO_3 (2 M) gave *N*-methylbenzamide (88% isolated yield), benzoic acid (100% isolated yield), and benzaldehyde (1% isolated yield, 5% by GC relative to *N*-methylbenzamide).

***N*-Methyl-*O*-benzylphenylacetohydroxamic Acid (13).** Compound **9** (330 mg, 2 mmol) was dissolved in 15 mL of methanol containing KOH (2 mmol). Benzyl bromide (342 mg, 2 mmol) was added and the solution stirred for 6 h at room temperature. The solution was poured into 25 mL of ethyl acetate and extracted with three 15-mL portions of 1 N NaOH, 20 mL of H_2O, and 15 mL of brine. Drying over $MgSO_4$ followed by filtration and evaporation gave **13** in 76% yield as a clear oil: NMR ($CDCl_3$) δ 3.16 (s, 3 H), 3.7 (s, 2 H), 4.73 (s, 2 H), 7.27 (s, 5 H), 7.37 (s, 9 H); mass spectrum (CI with CH_4) m/e 256 (M + 1).

Treatment of **13** (0.1 M) with $TiCl_3$ (0.2 M) in methanol–water (1:1) containing NH_4HCO_3 (2.5 M) and Na_2CO_3 (2 M) gave no reaction. Starting material was recovered in 96% yield after extractive workup.

***N*-(Benzyloxy)-3,3-dimethyl-2-azetidinone (3). Method A.** The procedure of Testa[22] (reaction of β-chloropivaloyl chloride and *O*-benzylhydroxylamine in pyridine at 100 °C), gave **3** in 59% yield: bp 95 °C (0.1 mmHg); IR (neat) 1780 cm^{-1}; NMR ($CDCl_3$) δ 1.2 (s, 6 H), 3.08 (s, 2 H), 4.95 (s, 2 H), 7.45 (s, 2 H); mass spectrum (CI with CH_4) m/e 206 (M + 1).

Method B. This method first involved preparation of *O*-benzyl-β-chloropivalohydroxamic acid by reaction of β-chloropivalic acid with *O*-benzylhydroxylamine with the water-soluble 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (WSC) in DMF–H_2O (1:4) at pH 4.5. The precipitated product (84%) was removed by filtration, dried, and cyclized to **9** in 94% yield by reaction with NaH in DMF at 20 °C for 1 h.

***N*-Methoxy-3,3-dimethyl-2-azetidinone (4)** was prepared by method A in 41% yield: bulb-to-bulb distilled; IR (neat) 1770 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (s, 6 H), 3.42 (s, 2 H), 3.82 (s, 3 H); mass spectrum (CI with CH_4) m/e 130 (M + 1).

***N*-Hydroxy-3,3-dimethyl-2-azetidinone (5)** was prepared quantitatively by hydrogenation of **3** with 10% Pd/C under 1 atm of H_2 in CH_3OH for 30 min. Compound **5** was an oil unstable to long storage (>1 week) at −20 °C and gave a negative $FeCl_3$ test: IR (neat) 1755 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (s, 6 H), 3.45 (s, 2 H), 8.57 (br s, OH); p*K* (titration) 6.85.

3,3-Dimethyl-2-azetidinone (25). *N*-Hydroxy lactam **5** (115 mg, 1 mmol) was dissolved in THF under N_2. A solution of 960 mg (6 mmol) of sodium acetate in 10 mL of H_2O was added followed by the dropwise addition of 20% $TiCl_3$ (2 mmol) in H_2O. After 2 h at room temperature the resulting suspension was poured into 25 mL of ethyl acetate, extracted with two 10-mL portions of 0.1 N NaOH and 20 mL of brine, dried over $MgSO_4$, filtered, and evaporated to give 78 mg (79% yield) of an oil which solidified upon storage in the freezer (−20 °C): mp ca. 20 °C (lit.[24] mp 28 °C); NMR ($CDCl_3$) δ 1.32 (6 H, s), 3.10 (2 H, s), 6.0 (br s, NH);[24] IR ($CHCl_3$) $\nu_{C=O}$ 1750, ν_{NH} 3450 cm^{-1}.

***O*-Benzyl-α-*N*-(*tert*-butoxycarbonyl)-L-serinehydroxamic Acid (30).**[1] *N*-Boc-L-serine (10 g, 49 mmol, Chemical Dynamics) was dissolved in 100 mL of THF. A solution of 15.6 g (98 mmol) of *O*-benzylhydroxylamine hydrochloride (Aldrich) in 400 mL of H_2O at pH 4.5 was added. The apparent pH was readjusted to 4.5 by dropwise addition of 50% NaOH. The pH was maintained at 4.5 with a Metrohm-Dossimat pH stat using 6 N HCl as the titrant while a solution of 20 g (98 mmol) of dicyclohexylcarbodiimide (DCC) in 300 mL of THF was added with stirring. A precipitate began to form immediately. After no more titrant was consumed (~3 h) the THF was removed in vacuo. The precipitate was removed by filtration and suspended in 300 mL of hot ethyl acetate. The insoluble dicyclohexylurea was removed by filtration and the ethyl acetate filtrate evaporated to give crude **30**. Purification by chromatography on silica gel (ethyl acetate) followed by recrystallization from ethyl acetate–hexanes gave 12.46 g (39 mmol, 79.5%) of **30**: mp 130–131 °C; $[\alpha]^{20}_D$ −37.7° (*c* 1.94, CH_3OH); NMR ($CDCl_3$) δ 1.45 (9 H, s), 3.65–4.67 (4 H, br m), 4.95 (2 H, s), 5.85 (1 H, d), 7.43 (5 H, s), 8.05 (1 H, br s); IR (KBr) 1650 cm^{-1} (C=O); mass spectrum (CI with CH_4) m/e 311 (M + 1).

Anal. Calcd for $C_{15}H_{22}N_2O_5$: C, 58.06; H, 6.77; N, 9.03. Found: C, 57.90; H, 7.00; N, 9.01.

Use of the water-soluble 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide (Sigma) in DMF–H_2O (1:4) at pH 4.5 for 30 min provided a more convenient but more expensive preparation of **30**. In this case only the desired product precipitated from the reaction solution. Simple filtration followed by recrystallization afforded **30** in 80–90% yield. Use of DCC and *N*-hydroxybenzotriazole in organic solvents without the addition of H_2O and control of the pH was not successful.

3-[(*tert*-Butoxycarbonyl)amino]-1-(benzyloxy)-2-azetidinone (6). Compound **30** (1.973 g, 6.4 mmol) and Ph_3P (1.7 g, 6.4 mmol) were dissolved in 40 mL of THF. While being stirred under nitrogen, a solution of diethyl azodicarboxylate (1.02 mL, 6.5 mmol, Aldrich) in 50 mL of THF was added dropwise. After the addition, the reaction was heated to 50 °C for 6 h. The solvent was then removed under reduced pressure and the residue chromatographed on silica gel (1:1 ethyl acetate–hexanes) to give 1.816 g of crude **6** contaminated with diethyl hydrazodicarboxylate. Rechromatography on TLC-grade silica (2:1 hexanes–ethyl acetate) under 8 lb of pressure followed by recrystallization from ethyl acetate–hexanes gave 1.148 g (3.96 mmol, 62%) of pure **6**: mp 91.5–92 °C; $[\alpha]^{20}_D$ −3.9° (*c* 2.65, CH_3OH); NMR ($CDCl_3$) δ 1.41 (9 H, s), 3.18–3.33 (1 H, dd), 3.55 (1 H, t), 4.33–4.5 (1 H, br), 5.0 (2 H, s), 5.13–5.47 (1 H, br), 7.48 (5 H, s); IR (KBr) 1700, 1760, 3310 cm^{-1}; mass spectrum (CI with CH_4) m/e 293 (M + 1).

Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.64; H, 6.85; N, 9.59. Found: C, 61.35; H, 6.80; N, 9.49.

3-[(*tert*-Butoxycarbonyl)amino]-1-hydroxy-2-azetidinone (26). Compound **6** (105 mg, 0.36 mmol) was dissolved in 10 mL of methanol and hydrogenated at 1 atm of H_2 in the presence of 10 mg of 10% Pd/C for 45 min. Filtration and evaporation gave 73.8 mg (0.36 mmol, 100%) of **26**. The compound was recrystallized from ether–hexanes: mp 122–124.5 °C dec; $[\alpha]^{20}_D$ −21.1 ± 1.6° (*c* 1.07, CH_3OH); NMR ($CDCl_3$) δ 1.45 (9 H, s), 3.41–4.08 (3 H, br m), 4.33–4.88 (1 H, br), 5.92–6.25 (1 H, br d); IR (KBr), 3310 (br), 1725, 1650 cm^{-1}; mass spectrum (CI with argon) m/e 203 (M + 1); p*K* = 6.5.

3-[(*tert*-Butoxycarbonyl)amino]-2-azetidinone (27). Compound **26** (433.5 mg, 2 mmol) was dissolved in 2 mL of CH_3OH and added to 18 mL of H_2O at pH 7.0. While the mixture was stirred under N_2 and the pH maintained at 7 with 3 N NaOH delivered by the pH stat as required, 6 mL (400 mol %) of a 20% aqueous solution of $TiCl_3$ (MCB) was added dropwise. After the addition was completed stirring was continued for 2 h. The aqueous mixture was then adjusted to pH 8 and extracted with three 25-mL portions of ethyl acetate. The combined ethyl acetate was washed with 10 mL of brine, dried over $MgSO_4$, filtered, and evaporated. The residue was recrystallized from ethyl acetate–hexanes to give 268.4 mg (1.4 mmol, 67%) of **27**: mp 173–175 °C; $[\alpha]^{20}_D$ −23.5° (*c* 1.27, CH_3OH); NMR ($CDCl_3$) δ 1.48 (9 H, s), 3.26–3.46 (1 H, dd), 3.63 (1 H, t), 4.67–5.06 (1 H, br), 5.2–5.58 (1 H, br), 6.08–6.33 (1 H, br); IR ($CHCl_3$) 3450 (s), 1770, 1590 cm^{-1}; mass spectrum (CI with CH_4) m/e 187 (M + 1).

Anal. Calcd for $C_8H_{13}N_2O_3$: C, 51.61; H, 7.53; N, 15.05. Found: C, 51.35; H, 7.78; N, 14.73.

Hydrolysis of 27 to L-2,3-Diaminopropionic Acid (28). Lactam **27** (86.6 mg, 0.465 mmol) was dissolved in 15 mL of 6 N HCl and refluxed for 3 h under N_2. After evaporation under reduced pressure the residue was recrystallized from water–ethanol to give 58.3 mg (86%) of the hydrochloride salt of L-2,3-diaminopropionic acid (DAPA, **28**): mp 225–230 °C dec; mmp [with authentic DAPA (Calbiochem)] 225–230 °C dec; $[\alpha]^{20}_D$ +22.5° (*c* 1.365, 1 N HCl); authentic L-DAPA $[\alpha]^{20}_D$ +25°;[15] amino acid analysis (short column), retention time 42 min (isographic with authentic L-DAPA).

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Registry No. 3, 71663-75-7; 4, 72229-72-2; 5, 71404-96-1; 6, 71405-00-0; 7, 72229-73-3; 2 (R, $R^2 = CH_3$), 7486-91-1; 2 (R^1 = BocNH, R^2 = H), 72229-74-4; 8, 495-18-1; 9, 72229-75-5; 10, 3532-25-0; 11, 959-32-0; 12, 16817-96-2; 13, 63820-45-1; 26, 71405-01-1; 27, 72229-74-4; 28, 1482-97-9; 30, 26048-92-0; 31, 72229-80-2; benzamide, 55-21-0; benzaldehyde, 100-52-7; ethyl phenylacetate, 101-97-3; *N*-methylhydroxylamine, 593-77-1; benzyl alcohol, 100-51-6; benzoic acid, 65-85-0; *N*-methylhydroxylamine hydrochloride, 4229-44-1; *N*-methylbenzamide, 613-93-4; benzyl bromide, 28807-97-8; *O*-benzyl-β-chloropivalohydroxamic acid, 72229-76-6; *N*-Boc-L-serine, 3262-72-4; β-chloropivaloyl chloride, 4300-97-4; *O*-benzylhydroxylamine, 622-33-3; *O*-benzylhydroxylamine hydrochloride, 2687-43-6; ethyl β-(benzyloxyamino)pivalate, 72229-77-7; β-(*N*-acetyl-*N*-benzyloxy)pivalic acid, 72229-78-8; 2,2-dimethyl-3-(benzyloxyamino)propanol, 72229-79-9; *N*-methylbenzeneacetamide, 6830-82-6; benzeneacetaldehyde, 122-78-1; β-chloropivalic acid, 13511-38-1.

Static and Flow Nuclear Magnetic Resonance of Dehydrohalogenation of 2-Chloropropanoyl Chloride[1]

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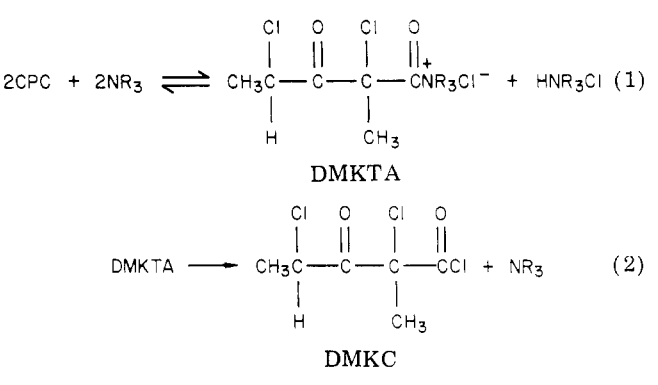
The dehydrohalogenation of 2-chloropropanoyl chloride (CPC) using diazabicyclooctane (Dabco) or triethylamine (TEA) in chloroform has been studied at temperatures ranging from 30 to −30 °C by using ^1H nuclear magnetic resonance spectroscopy under static and flowing conditions. In addition to several minor products, three species that have not been found previously are observed: $CH_3CHClCOCCl(CH_3)CClO$ (DMKC), $CH_3CHClCOCCl(CH_3)CO(NR_3)Cl$ (DMKTA), and 2,4-dichloro-2,4-dimethyl-1,3-cyclobutadione (DDC). For Dabco, the formation of DMKC from DMKTA is fast at 30 °C, and DMKTA cannot be detected above 0 °C. On the other hand, for TEA, DMKTA can be detected at 30 °C, and the formation of DMKC is slow, occurring over a period of several hours (depending on the TEA concentration). This decrease in rate allows the formation of DDC from DMKTA to become competitive. DDC is unstable in the reaction solution. Methylchloroketene appears to be a precursor of DMKTA; however, it is too reactive in the presence of base to be detected even by stopped-flow NMR at −30 °C. The presence of cyclopentadiene in the reaction mixture does not prevent the formation of DMKC when Dabco is used, but DMKC slowly decays with the resultant formation of the ketene–cyclopentadiene adduct. On the other hand, for TEA, this adduct is formed rapidly, and neither DMKTA nor DMKC is detected. Although the results appear different for the two bases, they can be accommodated by a common mechanism in which the rate of certain steps depends on the nature of the base.

The dehydrohalogenation of acyl halides using a base has been studied primarily by product analysis.[2-5] When the reaction is performed with 2-chloropropanoyl chloride (CPC) in the presence of triethylamine (TEA) and cyclopentadiene, *endo*- and *exo*-7-chloro-7-methylbicyclo[3.2.0]hept-2-en-6-ones (CMBH) are observed, indicating the presence of transient methylchloroketene. On the other hand, in the absence of cyclopentadiene, the ester, 1,2-dichloropropenyl-2-chloropropanoate (CCCP), is observed when a CPC/TEA concentration ratio of 2 is used in dry hexane.[2-4] In this case, CCCP is believed to form via reaction between the ketene and CPC. The tentative mechanisms suggested for these two reactions are based solely on product analysis. None of the possible intermediates have been detected, and no information concerning the time dependence of these reactions is available.

The present paper describes the study of the dehydrohalogenation of CPC as a function of time as well as the detection of a few transient species during the course of the reaction under various conditions using both static and flow proton nuclear magnetic resonance (NMR) at temperatures ranging from 30 down to −30 °C. For this purpose the solvent was changed from hexane to chloroform to simplify the NMR spectra and to avoid precipitation.

Scheme I



Two bases have been employed, TEA and diazabicyclooctane (Dabco), and although they differ in their effects on product distribution and on the time scale for the formation of certain products as well as on the lifetime of certain intermediates, it is possible to present a common mechanism that is consistent with the results obtained with either base. The main aspects of this mechanism involve

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