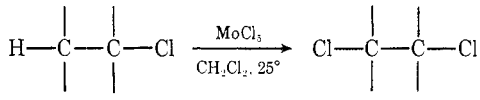
Vicinal Chlorination of Alkyl Chlorides with Molybdenum(V) Chloride[1]

Summary: The reaction of alkyl chlorides with an excess of molybdenum(V) chloride leads to vicinal chlorination in fair to excellent yields.

Sir: We wish to report that alkyl chlorides and haloalkanes in general react with an excess of molybdenum(V) chloride under mild conditions to produce vicinal dichloroalkanes in fair to excellent yields.[2] The preparation of 2,3-dichlorobutane illustrates a typical procedure. A solution of 2-chlorobutane (0.47 g, 5.0 mmol) in methylene chloride (7 ml) was added over an 8-min period to a vigorously stirred solution of molybdenum(V) chloride[3] (3.46 g, 12.7 mmol) in methylene chloride (6 ml) at room temperature with the rigorous exclusion of moisture and oxygen.[4] The resulting mixture was stirred for 8 hr. Direct chromatography of the reaction mixture over low activity alumina followed by analysis indicated the presence of *dl*-2,3-dichlorobutane (58%) and *meso*-2,3-dichlorobutane (38%). Results obtained on treatment of other representative halides are given in Table I.



This reaction sequence seems applicable to the vicinal chlorination of secondary and tertiary alkyl halides containing either a secondary or tertiary vicinal carbon. Primary alkyl chlorides are not chlorinated under these conditions.

Several specific points concerning the data in Table I deserve brief comment.

First, chlorination of alkyl chlorides appears to be regiospecific. Substitution is virtually exclusively vicinal and highly selective: tertiary vicinal carbons are chlorinated in exclusive preference to secondary vicinal carbons which in turn undergo chlorination in exclusive preference to primary vicinal carbons.

Second, chlorination is stereospecific. Cyclopentyl and cyclohexyl chloride yield exclusively *cis*-1,2-dichlorocyclopentane and *cis*-1,2-dichlorocyclohexane, respectively.

Third, vicinal chlorination is not limited to alkyl chlorides. Similar results, accompanied by halide–chloride exchange,[2] are obtained with alkyl bromides.

Fourth, the products of these reactions provide convincing evidence that vicinal chlorination with molybdenum(V) chloride does *not* proceed via the free-radical pathway characteristically observed in the chlorination of alkyl halides with molecular halogens and related halogenating agents. Specifically, chlorination with molybdenum(V) chloride occurs essentially exclusively at the carbon α to the halogen-bearing carbon.[5] In addition, vicinal chlorination of cyclopentyl and cyclohexyl chloride is unaccompanied by the formation of the respective *trans*-1,2-dichlorocycloalkane, typically observed when vicinal halogenation is performed using molecular halogen.[9,10]

Finally, chlorination of 2-chlorohexane yields, in addition to 2,3-dichlorohexanes, a substantial fraction of 3,4-dichlorohexane, indicating that, at least in this instance, chlorine migration has occurred. Such migration is reminiscent of the hydrogen migration observed during certain transition metal catalyzed olefin hydrogenations[11] and the thermal decomposition of certain transition metal alkyls.[12]

Table I
Vicinal Chlorination of Various Alkyl Halides with $MoCl_5$[a]

Alkyl halide (concn, *M*)	Products	Yield, %[b] (recovered RX, %)
2-Chlorobutane (0.4)	*meso*-2,3-Dichlorobutane	38
	dl-2,3-Dichlorobutane	58
Chlorocyclopentane (0.5)	*cis*-1,2-Dichlorocyclopentane	88
	trans-1,2-Dichlorocyclohexane	<1
Chlorocyclohexane (0.5)	*cis*-1,2-Dichlorocyclohexane	75
	trans-1,2-Dichlorocyclohexane	<1
3-Chloro-2-methylpentane (0.5)	2,3-Dichloro-2-methylpentane	46
2-Chloro-2,3-dimethylbutane (0.5)	2,3-Dichloro-2,3-dimethylbutane	40
1-Chlorooctane (0.5)	1,2-Dichlorooctane	<5 (>90)
2-Chlorohexane (0.4)	*erythro*-2,3-Dichlorohexane	1
	threo-2,3-Dichlorohexane	36
	dl-3,4-Dichlorohexane	14
	meso-3,4-Dichlorohexane	2
2-Bromobutane (0.3)	*meso*-2,3-Dichlorobutane	38
	dl-2,3-Dichlorobutane	54

[a] Unless otherwise indicated all additions were carried out in CH_2Cl_2 solution at room temperature under an inert atmosphere of dry nitrogen. The concentration of molybdenum(V) chloride was ~1.0 *M*. [b] Yields were determined by quantitative vapor phase chromatography and are based on alkyl halide.

These processes are believed to involve repetitive metal hydride elimination and addition steps. An analogous sequence of metal *halide* elimination and addition[13] may be involved in the overall reaction sequence leading to the formation of 3,4-dichlorohexane.

Further observations relative to the mechanism of these reactions will be presented in later papers.

References and Notes

(1) Supported by the Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society.
(2) The reaction of alkyl halides with a limiting amount of molybdenum(V)

chloride leads to halogen interchange: J. San Filippo, Jr., A. F. Sowinski, and L. J. Romano, *J. Org. Chem.*, **40**, 3295 (1975).
(3) A. J. Leffler and R. Penque, *Inorg. Syn.*, **12**, 187 (1970). Molybdenum(V) chloride is also available from several commercial sources.
(4) Molybdenum(V) chloride reacts rapidly with both water and molecular oxygen[3] and failure to exclude these substances leads to a diminished product yield.
(5) The relative reactivities of alkyl fluorides, chlorides, and bromides toward free-radical halogenation vary with the nature of the halide and the structure of the alkyl moiety. However, in general, carbons vicinal to the halogen-containing carbon are characterized by a *diminished* relative reactivity.[6] A particular exception is the free-radical bromination of alkyl bromides in which vicinal bromination is actually favored.[7,8]
(6) (a) W. A. Pryor, "Free Radicals", McGraw-Hill, New York, N.Y., 1966, Chapter 3; (b) C. Walling and M. F. Mayahi, *J. Am. Chem. Soc.*, **81**, 1485 (1959); (c) W. Thaler, *ibid.*, **85**, 2607 (1963); (d) W. Thaler, *Methods Free-Radical Chem.*, **2**, 166 (1970).
(7) P. S. Skell and P. D. Readio, *J. Am. Chem. Soc.*, **86**, 3334 (1964); J. G. Traynham and W. G. Hines, *ibid.*, **90**, 5208 (1968).
(8) P. S. Skell, R. R. Pavlis, D. C. Lewis, and K. J. Shea, *J. Am. Chem. Soc.*, **95**, 6735 (1973); K. J. Shea, D. C. Lewis, and P. S. Skell, *ibid.*, **95**, 7768 (1973), and references therein.
(9) G. A. Russel, A. Ito, and R. Konaka, *J. Am. Chem. Soc.* **85**, 2988 (1963); G. A. Russel and A. Ito, *ibid.*, **85**, 2983 (1963).
(10) As indicated by control experiments, *trans*-1,2-dichlorocyclohexane is not converted into *cis*-1,2-dichlorocyclohexane by $MoCl_5$ under reaction conditions.
(11) R. Cramer, *Acc. Chem. Res.*, **1**, 186 (1968).
(12) G. M. Whitesides, J. F. Gaasch, and E. R. Stedronsky, *J. Am. Chem. Soc.*, **94**, 5258 (1972), and references therein.
(13) Vicinal chlorination of olefins by molybdenum(V) chloride is known: J. San Filippo, Jr., A. F. Sowinski, and L. J. Romano, *J. Am. Chem. Soc.*, **97**, 1599 (1975).
(14) Exxon Summer Research Fellow, 1974.

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Received July 14, 1975

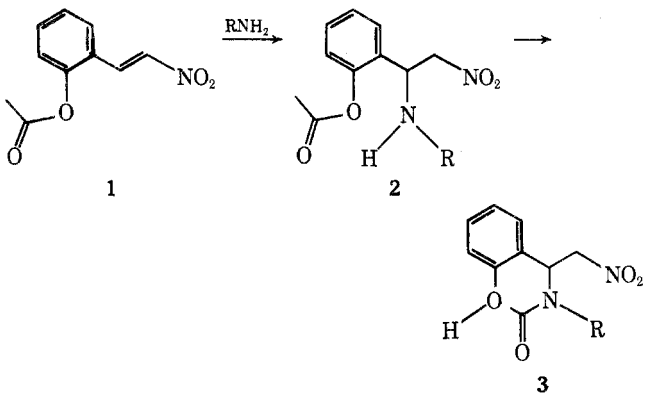
Anomalously Large Steric Inhibition of Intramolecular *O,N*-Acyl Transfer to Amino Acid Esters

Summary: Michael adducts of *o*-acetoxy-β-nitrostyrene and amino acid esters are found to undergo quantitative intramolecular, *O,N*-acyl transfer at anomalously slow rates; a model which rationalizes slow intramolecular acyl transfer to hindered amino acid derivatives is proposed.

Sir: Earlier,[1] we reported experiments demonstrating amide formation by intramolecular acyl transfer to an amine, trapped by a prior reaction with an electrophilic site. In the accompanying communication,[2] we apply this principle to peptide synthesis. Here we demonstrate and rationalize an unexpected, large steric inhibition of intramolecular *O,N*-acyl transfer which defines the scope of the principle.

In our earlier study, carbonyl functions were employed as amine trapping sites, and unwanted *O*-acyl transfer and dehydration were observed. To avoid these complications, we have investigated nitrostyrene derivatives. Reactions of **1** with primary amines yield Michael adducts in nearly quantitative yield;[3] rate constants fell in the range of 0.2 to 4 M^{-1} min^{-1}.[4]

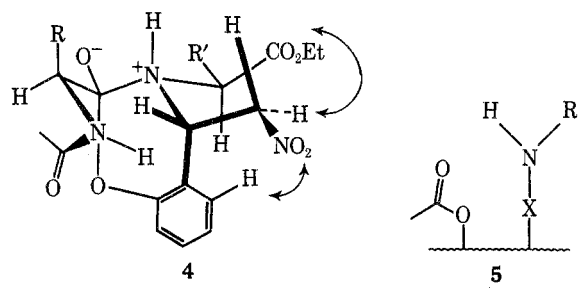
Most strikingly, the intramolecular *O,N*-acyl transfer, **2** → **3**, which can occur via an apparently favorable cyclic six-atom linkage, is slow and is subject to an exceedingly large steric effect. Thus, in acetonitrile a rate constant of 0.02 min^{-1} is observed at 25° for NH_2—R′=HGlyOEt, while for methyl esters of Ala, Phe, and Val, respective values of 2×10^{-4}, 7×10^{-5}, and 2×10^{-5} min^{-1} are observed. The rate ratios of 100 for Gly/Ala and 1000 for Gly/Val may be contrasted with the respective values of 4 and 10, observed for



the corresponding intermolecular aminolysis of *p*-nitrophenyl esters.[5]

Replacing acetoxy by carbobenzoxyglycyl resulted in no systematic change in acyl migration rate. More surprisingly, an attempt to buttress the acyloxy group by using 3,5-dibromo-2-acetoxynitrostyrene did not result in a significant change in acyl transfer rate or rate span. With alanine methyl ester **1** reacts to give two diastereomers, **2**, which rearrange to **3** at rates differing only by a factor of two.

A model which rationalizes the anomalous steric effect can be built from a successful model for steric effects on rates of aminolysis of peptide *p*-nitrophenyl esters.[5] Substitution of the additional linkages of **2** into the latter model yields **4** or a diastereomer as the structure of the



transition state for the conversion **2** → **3**. Steric interactions not shared with **2** or **3** arise in **4** between the nitromethylene group and the ester or alkyl substituent of the amine component. Stabilization of **4** through conformational changes is not possible, since the immediate environment of the carbon of the benzylamine moiety is bounded by the 3-H of the aromatic function, the alkyl substituent of the acyloxy function, and the nitromethylene group. The latter group encounters an interaction of the type found in a 1,3-diaxially substituted cyclohexane for any transition state **4** except that derived from glycine.

From this model, one predicts that anomalous steric sensitivity is expected for acyl transfer in all derivatives **5** except those in which the electrophilic site X is small and minimally substituted; e.g., for X equal to sulfur, methylene, or sp^2 carbon. In the accompanying communication we report normal transfer rates for a methylene system. [An attempt to prepare and study a sulfur case (derived from 1-acetoxy-2-chlorosulfenyl-4-chloronaphthalene) resulted in very slow transfer rates in an unhindered case (3×10^{-4} min^{-1} for HGlyOEt).]

Although it is difficult to envisage a practical reversible trapping involving an sp^2 electrophile, it was of interest to study acyl transfer in such a system, and ethyl esters of *N*-(2-acetoxyphenyl)glycine, alanine, and valine were prepared and studied.[6] Most surprisingly, *O,N*-acyl transfer in the unhindered Gly case is exceedingly sluggish, showing rate constants of 5.5×10^{-4} ($CDCl_3$), 5.0×10^{-4} (PhH),