Cation Radicals. II. Selectivity (>90%) for $\omega - 1$ Monochlorination of C_6 and C_8 Alcohols, Ethers, and Carboxylic Acids Using Nitrogen Cation Radicals

N. C. Deno,* W. Edward Billups,[1] Richard Fishbein,
Craig Pierson,[2] Robert Whalen, and John C. Wyckoff

Contribution from the Department of Chemistry,
The Pennsylvania State University, University Park, Pennsylvania 16802.
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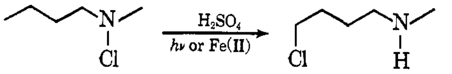
Abstract: Minisci showed that C_5–C_7 methyl esters, 1-chloroalkanes, and amines are chlorinated by R_2NCl *via* $R_2NH\cdot^+$ in 96% H_2SO_4. Fe(II) was used for initiation. This type of chlorination has been extended to alcohols, ethers, carboxylic acids, and amides using light in place of Fe(II) for initiation. These chlorinations are of unusual synthetic importance because (1) selectivity for the $\omega - 1$ position in C_6 and C_8 substrates is 90–92% in most cases, (2) selectivity for monochlorination is 90% with less than 5% polychloro products at 90% monochlorination, (3) alcohol and ether groups are totally protected from oxidation by protonation, (4) reactions are photochemical with exceptionally high quantum yields, (5) yields based on R_2NCl are 60–80%, and (6) the reactions offer a solution to the problem of converting monofunctional compounds to difunctional species in which the functional groups are widely separated.

The Hofmann–Löffler reaction is exemplified by eq 1. The mechanism has been established as proceeding *via* nitrogen cation radicals.[3–5] The extension to intermolecular chlorinations was first reported in a series of papers by Minisci.[6] Methyl esters of C_5–C_7 acids,[6] 1-chloroalkanes (C_4–C_6),[6] and hexylamine[7] were not only chlorinated by R_2NCl in concentrated sulfuric acid but the chlorinations showed high selectivity (70–80%) for the $\omega - 1$ position.


(1)

The present paper reports the extension of these chlorinations to 1-hexanol, 1-octanol, hexyl methyl ether, hexanoic acid, octanoic acid, and octanoamide using *N*-chlorodiisopropylamine. For a 1:1 ratio of R_2NCl to substrate, the results are summarized in Table I. The advantages and synthetic importance of these chlorinations are summarized in the abstract.

Mechanism. Minisci formulated the propagation steps as eq 2 and 3.[6] These are exact analogs of the propagation steps established for the intramolecular form of R_2HCl chlorination, the Hofmann–Löffler reaction.[3–5] Strong evidence for this formulation appeared in the work of Neale, who showed that the intermediate $R_2NH\cdot^+$ could be trapped by butadiene, chloroethylenes, and other alkenes.[8,9] Good yields of the addition products were obtained.[8,9]

$$R_2NH\cdot^+ + R'H \longrightarrow R_2NH_2^+ + R\cdot' \qquad (2)$$

$$R\cdot' + R_2NHCl^+ \longrightarrow R'Cl + R_2NH\cdot^+ \qquad (3)$$

Table I. $\omega - 1$ Chlorinations by *N*-Chlorodiisopropylamine at 25° and Using 1:1 Ratio of R_2NCl to Substrate

Substrate	% H_2SO_4 (solvent)	% yield (based on substrate consumed)[a] 2-Cl	3-Cl	4-Cl	5-Cl	6-Cl	7-Cl	8-Cl
1-Hexanol	72	0	2	2	*90*	6		
1-Octanol	72	0	2	1.5	1	3	*92*	0.5
	60	0	7	18	8	13	42	12
Hexyl methyl ether	96	tr	tr	tr	85	15		
	84	0	0	0	*92*	8		
Hexanoic acid	84[b]	0	0	6	*93*	1		
	60	10	5	22	45	18		
Octanoic acid	84[b]	0	0	0	5	14	*80*	1
	74[c]	0	0	4	11	29	55	1
Octanoamide	80	0	0	7	24	14	40	14
	50	0	2	8	13	11	*59*	8
	20	0	6	25	15	17	23	14

[a] Monochlorination of the substrate was 60–80% and the remainder was unchanged. [b] Similar results were obtained in 90% H_2SO_4. [c] Judging by the behavior of hexanoic acid in 60% H_2SO_4, chlorination would have been even more random at lower acidities.

It has been proposed that the chain-carrying species is Cl·, not $R_2NH\cdot^+$, and that R_2NCl serves only as a source of Cl_2.[10] Minisci's arguments[6] refuting this claim seemed adequate and have been supported.[11] The most decisive evidence against the Cl· proposal lies in coupling the data on $(i\text{-Pr})_2NCl$ chlorination (Table I) with data on Cl_2 chlorination,[12] both in 90% H_2SO_4. The distribution of products is entirely different. Citing only the major differences, $(i\text{-Pr})_2NCl$ gives 93% 5-chlorohexanoic acid whereas Cl_2 gives 40% 4-chloro and 42% 6-chloro.[12] With octanoic acid, $(i\text{-Pr})_2NCl$ gives 80% 7-chloro whereas Cl_2 gives 31% 4-chloro and 41% 8-chloro.[12] Preliminary results on Cl_2 chlorination of 1-octanol in 70% H_2SO_4 gave near random chlorination in contrast with the 92% 7-chloro-1-octanol obtained in chlorination by $(i\text{-Pr})_2NCl$. The propagation steps, eq 2 and 3, are thus established.

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* To whom all correspondence should be addressed.

(1) Shell Development Co. Fellow.

(2) National Science Foundation Fellow.

(3) M. E. Wolff, *Chem. Rev.*, **62**, 55 (1962).

(4) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 280.

(5) E. J. Corey and W. R. Hertler, *J. Amer. Chem. Soc.*, **82**, 1657 (1960).

(6) F. Minisci, G. P. Gardini, and F. Bertini, *Can. J. Chem.*, **48**, 544 (1970), and references cited therein.

(7) F. Minisci, *Chem. Ind. (Milan)*, 49, 947 (1967); *Chem. Abstr.*, **68**, 38796 (1968).

(8) R. S. Neale, *Tetrahedron Lett.*, 483 (1966); *J. Amer. Chem. Soc.*, **86**, 5340 (1964); R. S. Neale and R. L. Hinman, *ibid.*, **85**, 2666 (1963).

(9) R. S. Neale and M. R. Walsh, *ibid.*, **87**, 1255 (1965).

(10) D. D. Tanner and M. W. Mosher, *Can. J. Chem.*, **47**, 715 (1969).

(11) J. Spanswick and K. U. Ingold, *ibid.*, **48**, 546, 554 (1970).

(12) N. Deno, R. Fishbein, and J. Wyckoff, *J. Amer. Chem. Soc.*, **92**, 5274 (1970).

The initiation steps are not as firmly established. Photodissociation of R_2NHCl^+ to $R_2NH\cdot^+$ and $Cl\cdot$ had been accepted[3–5] for initiation of the Hofmann–Löffler reaction and naturally, Minisci was led to propose the same initiation for the intermolecular counterpart. Neale and Walsh[9] pointed out that R_2NHCl^+ does not absorb >300 mμ. They found that trace amounts of $RNHCl_2^+$ formed and disappeared during the reaction and proposed that photodissociation of $RNHCl_2^+$ initiated the process. We have found that visible light is sufficient catalyst, and it seems most likely that initiation is a combination of eq 4 and 5, particularly since traces of Cl_2 are known to be present.[9] It is also likely that eq 4 and 5 are the initiation steps in the Hofmann–Löffler reaction for the same reasons.

$$Cl_2 \xrightarrow{h\nu} 2Cl\cdot \tag{4}$$

$$Cl\cdot + RH \longrightarrow HCl + R\cdot \tag{5}$$

The Hofmann–Löffler reaction is often thermally initiated.[3] However, our attempts to use thermal initiation with *N*-chlorodibutylamine (a reported reaction[3]) failed. It is suspected that the supposed thermal initiations may in fact be initiation by adventitious light (quantum yields are unusually high, see below) or by traces of free radical generators such as peroxides.

Effect of Acidity on $\omega - 1$ Selectivity. The selectivity for $\omega - 1$ chlorination is much greater for $RCOOH_2^+$ and $RCONH_3^+$ than in their unprotonated counterparts (Table I). This is attributed to electrostatic repulsion between the positive charges on substrate and attacking radical ($R_2NH\cdot^+$).

Carboxylic acids are half-protonated in 80% H_2SO_4.[13,14] In 84 and 90% H_2SO_4, $RCOOH_2^+$ predominates and selectivity for the $\omega - 1$ position is excellent, 93% for the C_6 acid and 80% for the C_8 acid. In 60 and 74% H_2SO_4, RCOOH predominates and selectivity has largely disappeared.

Amides are half protonated in 25–30% H_2SO_4.[13] Correspondingly, R_2NCl chlorination in 50% H_2SO_4 is selective for the $\omega - 1$ position whereas in 20% H_2SO_4, selectivity has largely disappeared (Table I).

Esters are half-protonated in 80% H_2SO_4.[13] Correspondingly, Minisci[6] found selectivity for the $\omega - 1$ position for the methyl esters of C_5–C_7 and C_{10} acids in 96% H_2SO_4 whereas chlorination of methyl decanoate is 30% H_2SO_4 showed little selectivity.[11]

Alcohols and ethers are half protonated in 40-60% H_2SO_4.[13,15] Correspondingly, the $\omega - 1$ selectivity in 1-octanol was much greater in 70% H_2SO_4 than in 60% H_2SO_4 (Table I). In lower acidities, oxidation of the alcohol or ether function predominated,[16] and it is not possible to chlorinate the alkyl chain nor test the selectivity.

Substrate and $\omega - 1$ Selectivity. Greater $\omega - 1$ selectivity (>90%) is found with alcohols and ethers than with esters, carboxylic acids, or amides. This makes alcohols and ethers the substrates of choice for the production of α,ω difunctional species.

With primary alkyl ethers, H_2SO_4 concentrations from 65 to 96% are applicable. However, with primary alcohols, only a narrow range around 70% H_2SO_4 is applicable. Below 70% H_2SO_4, selectivity for the $\omega - 1$ position declines and ultimately oxidation of the alcohol group predominates. Above 70% H_2SO_4, (a) formation of alkyl hydrogen sulfate[17] complicates isolation of chloro alcohol, (b) decomposition to cyclopentenyl cations become a factor,[18] and (c) solutions darken which inhibits the photochemical process.

Butyric acid failed to chlorinate in 90% H_2SO_4, which is related to the absence of any sites sufficiently remote from the inhibiting $-COOH_2^+$ group.

Selectivity for Monochlorination. Chlorinations by R_2NCl are not only selective for the $\omega - 1$ position, but they are selective for monochlorination. Typically, a 1:1 ratio of R_2NCl to substrate gave 60–80% monochloro product, the remainder unreacted, and <5% dichlorinated. This was demonstrated both by boiling point of product and by gc analysis of the distillate. Octanoic acid was studied more extensively and 1.2 mol of R_2NCl gave 90% monochlorination with still <5% dichloro product.

This monochloro selectivity is a result of the fact that chlorination takes place remote from both the chloro substituents (as demonstrated by Minisci using 1-chloroalkanes[6]) and the protonated functional group. The monochloro product of a C_5–C_8 substrate will possess these inhibiting substituents at both ends of the molecule so that no CH_2 is remote from these inhibiting effects. The results stand in contrast to conventional chlorinations where good yields of monochloro products are achieved only at low conversions.

Experimental Section

Chlorination. Sunlamp irradiation was used instead of the Fe(II) used by Minisci.[6] As with the Hofmann–Löffler reaction, light and Fe(II) are interchangeable initiators. Chlorinations with 0.1 mol of R_2NCl were complete in 1 hr at 25° using sunlamp irradiation and a N_2 atmosphere.

***N*-Chlorodiisopropylamine.** This was prepared from diisopropylamine and *N*-chlorosuccinimide in ether at 25°.[19] *N*-Chlorination was complete in 1 hr and the succinimide was removed by filtration. Removal of ether *in vacuo* left crude R_2NCl, which was used without further purification. In fact, it may be advantageous to use unpurified *N*-chloroamine.[9]

Isolation of Products. Reaction mixtures were added to ice–water. The liquid organic layer was separated. Alcohols and ethers were directly distilled after drying. Carboxylic acids were converted to their methyl esters with $SOCl_2$ and CH_3OH before distillation. Amides were hydrolyzed to the acids by refluxing for 20 hr in 20% H_2SO_4 and then handled as with the acids.

Distillations were conducted at 20 mm. Wide ranges were collected to ensure inclusion of unreacted starting material and dichloro products for the gc analysis. It was noted in each case that the major fraction (monochloro product) had a boiling point in accord with boiling points reported for a representative isomer: 6-chloro-1-hexanol (108°, 12 mm),[20] 8-chloro-1-octanol (130°, 11 mm),[20] 4-chlorohexyl methyl ether (67°, 15 mm),[21] methyl 6-chlorohexanoate (100°, 16 mm),[22] and methyl 8-chlorooctanoate (133°, 16 mm).[23]

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[13] E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1963).

[14] N. Deno, C. U. Pittman, Jr., and M. J. Wisotsky, *J. Amer. Chem. Soc.*, **86**, 4370 (1964).

[15] R. E. Weston, Jr., S. Ehrenson, and K. Heinzinger, *ibid.*, **89**, 481 (1967).

[16] N. Deno and N. H. Potter, *ibid.*, **89**, 3550, 3555 (1967).

[17] N. Deno and M. S. Newman, *ibid.*, **72**, 3852 (1950).

[18] N. Deno, D. B. Boyd, J. D. Hodge, C. U. Pittman, Jr., and J. O. Turner, *ibid.*, **86**, 1745 (1964).

[19] H. Rushig, W. Fritsch, J. Achmidt-Thomé, and W. Haede, *Chem. Ber.*, **88**, 883 (1955).

[20] F. L. M. Patterson, W. C. Howell, A. J. McNamara, J. C. Schneider, and J. F. Walker, *J. Org. Chem.*, **21**, 739 (1956).

[21] R. L. Letsinger and A. W. Schnizer, *ibid.*, **16**, 704 (1951).

[22] F. Minisci and U. Pallini, *Gazz. Chim. Ital.*, **91**, 1030 (1961).

[23] L. D. Bergel'son, V. D. Solodovnik, and M. M. Shemyakin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 843 (1967); *Chem. Abstr.*, **67**, 99629 (1967).

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Analysis of Monochloro Acids. The methyl esters were analyzed by gc as described.[24] Methyl 7-chlorooctanoate was further identified by gc isolation and nmr spectrum: 1.50 (d, $J = 6$ cps, CH_3), 2.25 (t, $J = 7$ cps, α-CH_2), 3.62 (s, $-OCH_3$), and 3.90 (sextet, $J = 6$ cps, $-CHCl-$). The doublet at 1.50 and the sextet at 3.90 in the ratio 3:1 are unique features of methyl 7-chlorooctanoate and would not be found in any of the other six isomeric methyl monochlorooctanoates.

Analysis of Monochloro Alcohols. The mixtures of monochloro alcohols were oxidized to the monochlorocarboxylic acids by heating with 70% HNO_3 for 1 hr at 100°. Traces of $NaNO_2$ were added to initiate oxidation. Yields from the oxidation were near quantitative. The monochlorocarboxylic acids were converted to methyl esters and analyzed by gc as described above.

The same analysis could be obtained by direct gc of the alcohols using the same column as with methyl esters. Like the methyl esters, retention times increased with increasing separation of the chloro substituent and the functional group. The precision was not as good because of broader bands and some tailing.

Analysis of Monochloro Ethers. The same gc column was used as with the methyl esters. It was assumed that retention times increased with separation of chloro substituent and ether function. The identification of the major (92%) product, 5-chlorohexyl methyl ether, was supported by the nmr spectrum of a gc isolated sample: δ 0.8–1.8 (m, CH_2), 1.45 (d, $J = 6$ cps, CH_3), 3.20 (s, $-OCH_3$), 3.2–3.5 (m, $-CH_2O-$), and 3.95 (sextet, $J = 6$ cps, $-CHCl-$). The 1.45 doublet and 3.95 sextet were unique features of 5-chlorohexyl methyl ether and would not be found in the other five isomeric monochlorohexyl methyl ethers.

Analysis of Monochlorooctanoamides. These were converted to the methyl monochlorooctanoates for analysis.

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[24] N. Deno, R. Fishbein, and C. Pierson, *J. Amer. Chem. Soc.*, **92**, 1451 (1970).

Electrophilic Additions to 2-Methyl-1-(tetramethylcyclopropylidene)propene. Generation of Cyclopropylidenecarbinyl Cations

Marvin L. Poutsma* and Pedro A. Ibarbia

Contribution from Union Carbide Research Institute,
Union Carbide Corporation, Tarrytown, New York 10591.

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Abstract: Allene **8** undergoes protonic attack largely at a *terminal* carbon atom, in contrast to other tetraalkylallenes, because of special stabilization of vinyl cation **12** by the cyclopropane ring. The major products (isomer **9** and adducts **10a–d**) contain the structure of ring-opened cation **11** but products related to cation **12** (**22c** and **23**) have been detected. A minor protonation route is normal *central* attack which gives cation **17** followed by (or synchronous with) electrocyclic ring opening to cation **18** and ultimate formation of triene **15**; the latter is the major acid-catalyzed rearrangement product of diene **13**, formed from **8** under basic conditions. Chlorination (product **24**), bromination (products **25–32**), and addition of chlorosulfonyl isocyanate (product **33**) also occur by predominant terminal electrophilic attack. However, epoxidation gives adduct **36** and acetoxymercuration in methanol gives adduct **39**, each with attachment of the electrophilic species at the central carbon atom of **8**. In these cases, nucleophilic opening of a bridged cation is postulated as the product-determining step.

Electrophilic additions to allenes[1] can give two possible product orientations (**1** or **2**) dependent on allene and electrophile structure. Addition of protonic acids to allene itself gives adducts of structure **1** by terminal attack, presumably *via* a vinyl cation (**3**),[2,3] rather than by central attack *via* an allyl cation (**4**). Even though cation **4** is surely more stable than cation **3**, it was pointed out[2a] that the transition state for central attack (**5**) must largely maintain the twisted allene geometry and hence a better model for it would be an α-vinyl primary cation. However, addition of potentially bridging electrophiles such as the halogens[4a,b] or sulfenyl halides[2a,4c] gives type **2** products even for the parent allene. As alkyl groups are substituted on the allenic bond, the path leading to **2** becomes more and more favored for nonbridging electrophiles owing to stabilization of transition state **5**. Thus tetramethylallene (**7**) gives type **2** products with hydrogen halides,[5] halogens,[6] sulfenyl halides,[4c] mercuric salts,[7] peracids,[8] and chlorosulfonyl isocyanate.[9] We report herein the unusual behavior of 2-methyl-1-(tetramethylcyclopropylidene)propene (**8**)[10] toward electrophilic reagents, compared to **7** as a model for tetraalkylallenes. While our work was in progress, Crandall and coworkers[11] reported that allene **8** reacted with acetic acid–sulfuric acid to produce a mixture of 2,3,3,6-tetramethyl-1-hepten-4-yne (**9**), 2,3,3,6-tetramethyl-4-heptyn-2-ol (**10a**), and the corresponding acetate (**10b**), all products containing the

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[1] D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967); K. Griesbaum, *Angew. Chem., Int. Ed. Engl.*, **5**, 933 (1966).

[2] (a) T. L. Jacobs and R. N. Johnson, *J. Amer. Chem. Soc.*, **82**, 6397 (1960); (b) K. Griesbaum, W. Naegele, and G. G. Wanless, *ibid.*, **87**, 3151 (1965); (c) K. Griesbaum, *Angew. Chem., Int. Ed. Engl.*, **8**, 933 (1969).

[3] P. J. Stang and R. Summerville, *J. Amer. Chem. Soc.*, **91**, 4600 (1969).

[4] (a) H. G. Peer, *Recl. Trav. Chim. Pays-Bas*, **81**, 113 (1962); (b) W. H. Mueller, P. E. Butler, and K. Griesbaum, *J. Org. Chem.*, **32**, 2651 (1967); (c) W. H. Mueller and P. E. Butler, *ibid.*, **33**, 1533 (1968).

[5] J.-P. Bianchini and A. Guillemonat, *Bull. Soc. Chim. Fr.*, 2120 (1968).

[6] M. L. Poutsma, *J. Org. Chem.*, **33**, 4080 (1968).

[7] W. L. Waters and E. F. Kiefer, *J. Amer. Chem. Soc.*, **89**, 6261 (1967).

[8] J. K. Crandall and W. H. Machleder, *ibid.*, **90**, 7292 (1968).

[9] E. J. Moriconi and J. F. Kelly, *J. Org. Chem.*, **33**, 3036 (1968).

[10] H. D. Hartzler, *J. Amer. Chem. Soc.*, **83**, 4990 (1961).

[11] J. K. Crandall, D. R. Paulson, and C. A. Bunnell, *Tetrahedron Lett.*, 5063 (1968).