A Remarkably Efficient Markovnikov Hydrochlorination of Olefins and Transformation of Nitriles into Imidates by Use of AcCl and an Alcohol

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Dedicated fondly to Professor Dr. Hiriyakkanavar Ila on the occasion of her 60th birthday

Keywords: Acetyl chloride / Alcohols / Markovnikov hydrochlorination / Nitrile-imidate transformation

HCl generated by mixing AcCl with EtOH brings about Markovnikov hydrochlorination of olefins in excellent yields. The products are isolated in states of high purity simply by removal of the volatile components under reduced pressure. Further, nitriles are transformed into imidate hydrochlorides on similar treatment with AcCl and an alcohol. This procedure for nitrile-imidate transformation is much more efficient than that used previously, which involved continuous passing of HCl gas into the solution of a nitrile in a solvent such as Et_2O or benzene and an alcohol until one equivalent had been absorbed.

Introduction

Hydrochlorination of olefins is of fundamental interest, and several methods to achieve this transformation have been designed. Gaseous HCl does not add to monosubstituted olefins at a preparatively useful rate,[1] but addition proceeds well when the olefin is highly substituted,[2] part of a styryl system[3] or strained.[4] Liquefied HCl adds to cyclohexene in the presence of Me_3Al in good yield.[5] 1-Methylcyclohexene, however, did not give the desired product, instead furnishing 1,1-dimethylcyclohexane. Lipophilic phosphonium salts catalysed hydrochlorination of mono- and 1,2-disubstituted olefins with aqueous HCl under phase-transfer conditions in good yields at elevated temperatures,[6,7] but chromatographic purification of the product was unavoidable. Mixed olefin-carbonyl complexes of Pt^{II} catalyse addition of HCl to olefins, though the reaction is slow.[8] Appropriately prepared Al_2O_3 and SiO_2 have been used to promote addition of HCl generated in situ from the hydrolysis of various organic and inorganic chlorides by adventitious water.[9] The reaction times were generally long and the yields were low to moderate. Zeolite ZF520, K10 montmorillonite[10a] and SiO_2[10b] together with $SOCl_2$ have also been employed as sources of HCl for additions to olefins. Water has been added to reactive chlorides such as $SOCl_2$ and Me_3SiCl (rather than depending on the water bound to solid surfaces) to generate HCl, which added slowly to a wide range of olefins in 65–90% yields.[11]

Imidates are an important class of compounds that find application in the preparation of *s*-triazines,[12] 1,2,4-triazoles,[13] 1,2,4-oxadiazoles,[13] diazirines,[14] selenoesters,[15] selenoamides[15] and 2-substituted pyrimidin-4-(3*H*)-ones,[16] and also in the conversion of pyrimidine into pyridine.[17] As important as these substances are, experimentally convenient methods for their preparation are unfortunately unavailable. The imidates have customarily been prepared by passing HCl gas into a solution of a nitrile and an alcohol in a solvent such as benzene or ether until one equivalent had been absorbed. Stirring was continued until the precipitation of the imidate hydrochloride was complete (16–24 h), and the salt was collected and treated with a base to isolate the corresponding imidate.

The generally low yields, tedious experimental procedure, longer reaction time, need for chromatographic purification and requirement of speciality or less readily available chemicals prompted us to devise alternative methods both for the hydrochlorination of olefins and for the transformation of nitriles into imidates. While lecture bottles of HCl are convenient, the bottle itself must be handled cautiously because of the corrosive nature of its contents, and methods to generate HCl in the laboratory are cumbersome. Generation of HCl in situ is thus appealing, and it may be primarily for this reason that several such methods have been discovered in the past.[9–11]

AcCl is relatively cheap and more readily available than any of $SOCl_2$, Me_3SiCl, Zeolite ZF520 and K10 montmorillonite. These considerations prompted us to explore HCl generation from AcCl by treatment with an alcohol. Very recently, we have demonstrated the use of EtOH/AcCl combinations as a convenient source of HCl to transform allyl acetates and allyl alcohols into allyl chlorides.[18] The AcCl/

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Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

DOI: 10.1002/ejoc.200400591

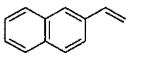
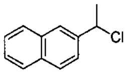
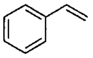
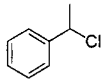
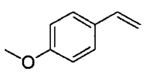
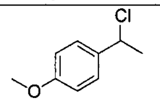
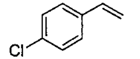
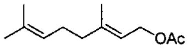
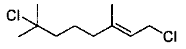
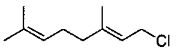
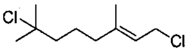
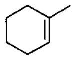
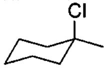
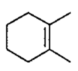
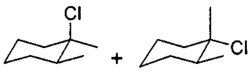
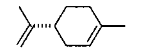
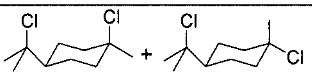
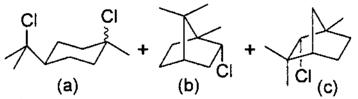
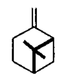
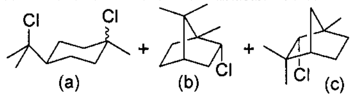
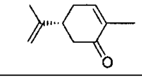
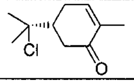
alcohol combination could, in principle, be used for other reactions as well, and here we demonstrate the AcCl/alcohol combination as an effective reagent for: (a) hydrochlorination of olefins, and (b) facile transformation of nitriles into imidates.

Results and Discussion

The results of the hydrochlorinations are collected in Table 1. The olefins that generated more stable benzylic and tertiary carbocations on Markovnikov protonation reacted rapidly to furnish products in high yields. For instance, 2-vinylnaphthalene and 4-methoxystyrene underwent smooth reaction in 75 min and 10 min, respectively, whereas the less electron-rich parent styrene and 4-chlorostyrene reacted very slowly. Mono- and 1,2-disubstituted olefins such as 1-decene and cyclooctene, respectively, did not react at all (not shown). Interestingly, geranyl chloride added HCl across the remote double bond only (entry 6) and no addition of HCl across the double bond of the allyl chloride unit occurred even though it was trisubstituted. Similar observations had also been made earlier by Julia and Roy.[21]

1,2-Dimethylcyclohexene (entry 8) reacted rapidly to generate a 91:9 mixture of *trans*- and *cis*-1-chloro-1,2-dimethylcyclohexane. In order to investigate the mechanism of addition, aliquots were withdrawn and analysed for product distribution. The change in the ratio of the *trans*- and *cis*-1-chloro-1,2-dimethylcyclohexanes with reaction time is given in Figure 1. The predominance of *trans* isomer at the very beginning of the reaction suggests predominantly *trans* addition; the small amount of *cis* isomer that was formed during the course of the reaction isomerizes to the *trans* isomer. The reaction should thus involve Markovnikov protonation of olefin and preferential capture of the resultant cation by chloride ion from the axial face. Alternatively, a protonium ion could be formed, opening in 1,2-diaxial manner on chloride ion attack to furnish the observed predominant product. In the past, addition of HCl to olefins has been carried out in Et_2O, pentane, MeOH, AcCl and

Table 1. Markovnikov hydrochlorination of olefins with AcCl/EtOH

Entry	Substrate	Time (min)	Product(s)	Yield (%)	Ref
1		80		97	19
2		840		98	
3		10		98	20
4		360	–	–[a]	
5		15		95	
6		15		96	21
7		20		94 [b]	9b
8		10		96 [b, c]	9b
9		10		95 [b, d]	22
10		15		95 [b, e]	9b, 23
11		15		94 [f]	
12		90		96	11

[a] Only trace amount of the product was formed after 6 h. [b] AcCl was added at 0 °C. [c] The ratio of *ax*:*eq* chlorides by ^1H NMR spectroscopy was 10:1. [d] The ratio of *ax*:*eq* chlorides by ^1H NMR spectroscopy was 4.5:1. [e] *a*:*b*:*c* = 3.1:1.3:1. [f] *a*:*b*:*c* = 4.6:1.3:1.

CH_2Cl_2 or in the absence of a solvent. The addition was predominantly *trans* in Et_2O (95:5),[2b][2c] pentane (92:8)[2a] and MeOH (95:5)[2a] and *cis* in AcCl (76:24)[2a] and CH_2Cl_2 (88:12).[2b,2c]

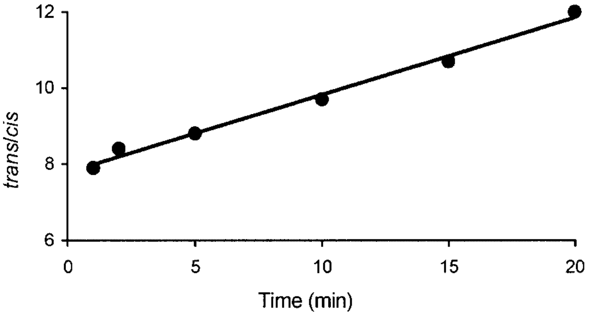
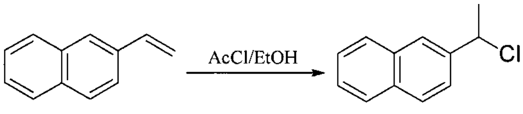


Figure 1. Change in *trans*/*cis* ratio with time (slope: 0.203 min^{-1})

The reaction of (*R*)-(+)-limonene produced a 4.5:1 mixture of two dichlorides (entry 9). The predominant product was the more stable conformer with axial chlorine.[22] Both α-pinene and β-pinene furnished the same product mixture, consisting of limonene hydrochloride, *endo*-2-chloro-1,7,7-trimethylbicyclo[2.2.1]heptane and *endo*-2-chloro-1,3,3-trimethylbicyclo[2.2.1]heptane. Limonene hydrochloride, however, was the major product in both instances.

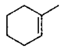
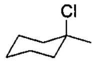
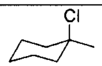
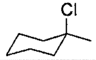
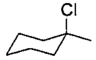
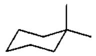
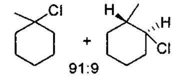
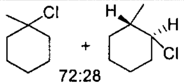
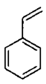
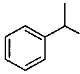
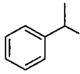
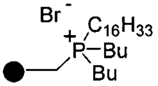
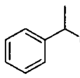
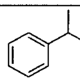
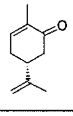
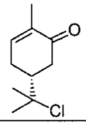
The poor reactivity of 1,2-disubstituted and electron-deficient olefins with AcCl/EtOH offered the promise of chemoselective hydrochlorination of electron-rich olefins. Indeed, addition of HCl to carvone (entry 12) was fully chemoselective as it took place only at the more electron-

Table 2. Effect of excess EtOH on the efficiency of hydrochlorination



Ethanol (equiv.)	AcCl (equiv.)	Time (min)	% Starting material reacted
08	08	80	100
24	08	80	65
40	08	80	19

Table 3. A comparison of the new method with literature procedures for Markovnikov hydrochlorination of olefins

Entry	Substrate	Reagent/solvent	HCl precursor	Time	Temp (°C)	Product(s)	Yield (%)	Ref
1		no catalyst	EtOH-AcCl	20 min	25		94	–[a]
		no catalyst/DCM	HCl (gas) [b]	1 h	-78		90	9
		Al_2O_3/DCM	AcCl	2 h	25		31	9 [c]
		SiO_2/DCM	AcCl	2 h	25		81	9 [c]
		Me_3Al/EtCl	liquified HCl	30 min	-50		92 [d]	5
		K10 montmorillonite/ DCM	$SOCl_2$	21 h	25		100	10(a)
		no catalyst/DCM	$SOCl_2$	21 h	25		20	10(a)
2		no catalyst	EtOH-AcCl	14 h	25		98	–[a]
		$R_4P^+Br^-$	HCl (aqueous)	1 h	115		90	6
			HCl (aqueous)	5 h	50		98	7
		no catalyst	Me_3SiCl-H_2O	10 h	25		86	11
3		no catalyst	EtOH-AcCl	1.5 h	25		96	–[a]
		no catalyst	Me_3SiCl-H_2O	20 min	25		84	11

[a] This work. [b] Gaseous HCl was continuously bubbled into the solution. [c] Al_2O_3 and SiO_2 adsorbents were equilibrated with atmospheric moisture at 120 °C for a minimum of 48 h prior to use. [d] No chlorinated product was formed.

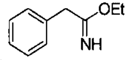
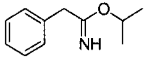
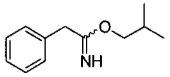
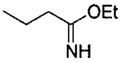
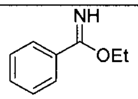
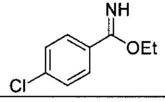
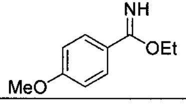
rich olefin. The AcCl/EtOH combination is thus suitable for the chemoselective hydrochlorination of electron-rich trisubstituted and styryl olefins in the presence of electron-deficient and mono- and 1,2-disubstituted olefins.

We wished to explore the influence of excess EtOH on the efficacy of the above hydrochlorination and so we studied the reaction behaviour of 2-vinylnaphthalene with different AcCl/EtOH ratios (Table 2). The reaction was complete within 80 min when 8 equivalents each of AcCl and EtOH were used (Entry 1), but was only 65% complete after 80 min when 8 equivalents of AcCl and 24 equivalents of EtOH were used (entry 2). Further, the reaction was only 19% complete after 80 min when 8 equivalents of AcCl and 40 equivalents of EtOH were used. Thus, excess EtOH retarded the reaction. This may tentatively be due to solvation of H^+ by EtOH, lowering its electrophilicity. The percentage of the reacted starting material was calculated from the relative ^1H integrals of the terminal olefinic protons in the starting material and the C*H*Cl in the product.

Table 3 presents a comparison of the efficiency of the new procedure with literature methods. It is clear that the new method is generally superior to others as far as the hydrochlorination of trisubstituted olefins is concerned. Though the reaction between 1-methylcyclohexene and K10 montmorillonite/$SOCl_2$ is quantitative, it takes relatively a very long time and also generates a mixture of both the Markovnikov and the *anti*-Markovnikov products. The new method takes slightly longer than the procedure with Me_3SiCl/H_2O as the source of HCl for the chemoselective hydrochlorination of carvone. The yield, however, is slightly better with the new method. Although the reason is not understood at present, the AcCl/EtOH method was very slow in the hydrochlorination of styrene (entry 2) in comparison to other methods; it took 14 h until completion. In contrast, *p*-methoxystyrene had reacted completely within 10 min (Table 1).

The results of the reactions of different nitriles with selected alcohols and AcCl are collected in Table 4. The optimum nitrile/AcCl/alcohol ratio for a preparative-scale reaction was 1:8:12. The formation of an imidate from a primary alcohol was relatively faster than from a secondary alcohol. The reaction of benzonitrile was slower than that of benzylnitrile. This may be due to the enhanced stability of the vinyl cation formed by protonation of nitrogen thanks to conjugation with the aromatic ring. The presence of electron-donating groups on the aromatic ring would therefore be expected to retard the reaction further. Indeed, the ratio of the rates of the reactions of *p*-methoxybenzonitrile and of benzonitrile was 45:55. Slightly electron-withdrawing groups on the aromatic nucleus could be tolerated, allowing the reaction to proceed. For instance, *p*-chlorobenzonitrile reacted more slowly than *p*-methoxybenzonitrile, the relative rate ratio being 40:60. (The relative reaction rates were calculated from ^1H integrals of product mixtures obtained from competitive reactions of equimolar mixtures of two nitriles.) More strongly electron-withdrawing substituents on the aromatic ring are therefore likely to be detrimental to imidate formation; *p*-nitrobenzonitrile, for instance, did not react. A tentative reason for this complete failure may be the failure of protonation of nitrogen due

Table 4. Reactions of different nitriles with AcCl and selected alcohols

Entry	Substrate	Alcohol	Time (h)	Product	Rxn (%)[a]	Yield (%)
1	$PhCH_2CN$	EtOH	6		100	95
2	$PhCH_2CN$	*i*PrOH	11		100	95
3	$PhCH_2CN$	*i*BuOH	7		100	93[b]
4	$CH_3CH_2CH_2CN$	EtOH	6		100	85
5	C_6H_5CN	EtOH	16		100	94
6	*p*-Cl-C_6H_4CN	EtOH	13		100	94
7	*p*-NO_2-C_6H_4CN	EtOH	12	–	–	–[c]
8	*p*-MeO-C_6H_4CN	EtOH	18		100	95

[a] Reaction% indicates the percentage of the starting material reacted. [b] Ratio of the isomers was 1.4:1. [c] Only a trace amount of the product was formed.

to the strong electron-withdrawal toward the aromatic ring caused by the nitro function, resulting in less efficient (or no) formation of the requisite vinyl cation.

Conclusion

In summary, use of the AcCl/EtOH combination (8 equivalents each) brings about the transformation of olefins into Markovnikov hydrochlorides in high yields with a considerable shortening of reaction time in an operationally convenient procedure (see Exp. Sect.). Chromatographic purification is not generally necessary, as the product obtained from removal of volatiles is pure enough to be used directly in subsequent synthetic manoeuvres. This procedure is also effective for the transformation of nitriles into imidates in excellent yields over timespans generally shorter than reported previously (see Exp. Sect.). Since this method generates HCl in situ, it obviates the dangerous nuisance of corroded/frozen valves that is often experienced with lecture bottles. The additional convenience of the clean transformation of the initial solvent-cum-reactant into an inert and easily removed solvent-cum-product is alchemical wizardry at its best.[24]

Experimental Section

General Procedure for the Hydrochlorination of Olefins: AcCl (8 mmol, 0.57 mL) was added dropwise to a solution of olefin (1 mmol) in dry EtOH (8 mmol, 0.47 mL). The reaction flask was stoppered tightly and the stirring was continued at 30 °C. After the reaction was complete by TLC, the unchanged AcCl and EtOH, if any, and the EtOAc that had formed from the reaction of EtOH with AcCl were removed under reduced pressure to obtain the product.

General Procedure for the Preparation of Imidates: AcCl (8 mmol, 0.57 mL) was added to a stirred solution of a nitrile (1 mmol) and an alcohol (12 mmol). The reaction flask was stoppered tightly and the stirring was continued at 25 °C. After the reaction was complete by TLC, the volatiles were removed under reduced pressure to isolate the imidate hydrochloride. Alternatively, the reaction mixture was cooled to 0 °C and mixed slowly with saturated aqueous $NaHCO_3$ solution, until gas evolution had ceased. The product was extracted into Et_2O (3 × 5 mL) and the organic solution was washed with H_2O (1 × 5 mL) and brine (1 × 5 mL) and concentrated under reduced pressure to obtain the imidate.

Supporting Information: ^1H, ^{13}C and analytical data on several of the compounds prepared in this study (see also the footnote on the first page of this article).

Acknowledgments

The authors thank the Council of Scientific & Industrial Research, Government of India, for financial support. KGB thanks CSIR, and AG thanks UGC for the award of a Senior Research Fellowship and a Junior Research Fellowship, respectively.

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Received August 19, 2004