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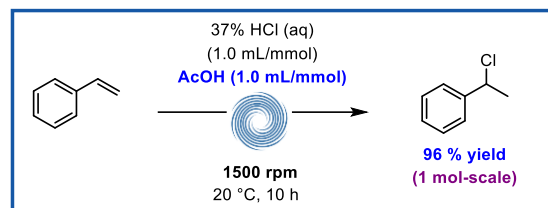
Hydrochlorination of alkenes with hydrochloric acid

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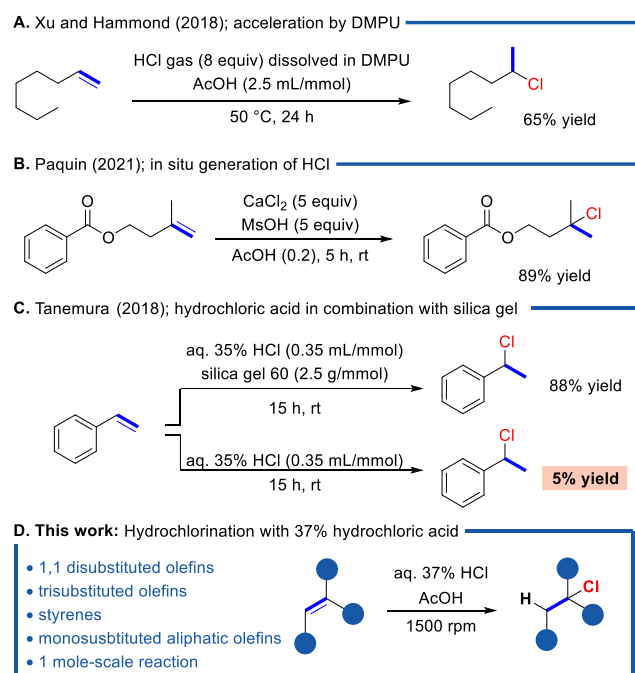


ABSTRACT: The hydrochlorination of alkenes with hydrogen chloride gas is typically limited to activated olefins. Herein, we present an innovative hydrochlorination approach utilizing hydrochloric acid within vigorously agitated solutions. Notably, the introduction of acetic acid was found to enhance the reaction rate. We substantiated the practicality of our method by conducting the hydrochlorination of styrene on a one mole scale with a 96% yield.

KEYWORDS: alkenes, hydrochlorination, hydrochloric acid, mol-scale reaction

Alkyl chlorides exhibit versatile properties that greatly enhance their utility in organic synthesis. As electrophiles, they find application in substitution reactions, while metal insertion enables their transformation into nucleophiles.¹ Furthermore, they actively engage in radical reactions, cross-coupling processes, and eliminations.² Since Markovnikov's initial discovery,³ the hydrochlorination of 1,1-disubstituted alkenes with hydrogen chloride gas has been established to access tertiary alkyl chlorides. Conversely, hydrochlorination of monosubstituted alkenes continues to present a challenge, primarily due to their sluggish reactivity but also the formation of regioisomeric mixtures as a result of hydride or alkyl migrations.^{4,5} Moreover, the utilization of HCl gas on a laboratory scale can pose safety concerns arising from corroded gas cylinders. In order to address these challenges, recent reports have emerged, centering on several approaches: a) enhancing reaction rates through the utilization of condensed hydrogen chloride,⁶ metal catalysts,^{7,8} or DMPU as a solvent⁹ (e.g. Scheme 1A); b) exploration of alternative routes for hydrogen chloride generation (e.g. Scheme 1B);^{4,10–15} c) cobalt¹⁶ and iron^{17,18} catalyzed radical hydrochlorination reactions; d) anti-Markovnikov hydrochlorination^{19–21}. In our current investigations, we required secondary and tertiary alkyl chlorides on a multi-gram scale, and we sought a straightforward hydrochlorination protocol that eliminates the need for hydrogen chloride gas. Surprisingly, hydrochloric acid, a readily available bulk chemical, is rarely employed for hydrochlorination reactions. Two notable studies by Rolla²² and Tanemura²³ (e.g. Scheme 1C), utilizing phase transfer catalysts or silica gel activation respectively, have demonstrated that hydrochlorination reactions can be carried out with hydrochloric acid, albeit often requiring several days for complete conversion. Tanemura also reported that the reaction with hydrochloric acid in the absence of silica gel is inefficient (5% yield; Scheme 1C). Our aim was to revisit the hydrochlorination of alkenes using simple hydrochloric acid. The challenge was to identify reaction conditions and additives that would significantly increase the reaction rates (Scheme 1D).

Scheme 1. Previous work; selected examples.



We commenced our investigations with 1-methyl-1-cyclohexene (alkene **1**) and surveyed the role of stoichiometry (Table 1). Our initial experiment using 1.2 equivalents of hydrochloric acid at room temperature (rt) for 20 min, afforded tertiary chloride **2** within just 20 minutes, albeit with a low 11% yield (entry 1). When we increased the hydrochloric acid quantity from 0.1 mL to 2.0 mL per mmol of alkene, the GC-yield reached 84% (entries 2–4). Based on previous reports by Hammond⁹ and Paquin¹⁴ and recent DFT studies by Xu²⁴, we added acetic acid in various amounts to the reaction mixture. Indeed, the inclusion of 0.5 mL of acetic acid increased the yield from 61% (entry 2) to 96% (entry 5). In accordance with the conditions outlined in

entry 5, we conducted a large-scale reaction (0.1 mol of **1**) and obtained pure chloride **2** in an 81% yield. Further exploration of HCl and acetic acid amounts revealed that equimolar volumes of both reagents yield optimal results (entries 6-9). From the start, we worked with a high stirring speed (1500 rpm). Decreasing this speed to 0, 500, and 1000 rpm resulted in a sharp decrease in GC-yield (entries 10-12, Table 1).

Table 1: Optimization of reaction conditions,^a

| entry | HCl (mL/mmol) | additive (mL/mmol) | rpm ^b | yield (2) (%) ^c |
|-------|---------------|--------------------|------------------|-------------------------------------|
| 1 | 0.1 | none | 1500 | 11 |
| 2 | 0.5 | none | 1500 | 61 |
| 3 | 1.0 | none | 1500 | 81 |
| 4 | 2.0 | none | 1500 | 84 |
| 5 | 0.5 | AcOH (0.5 mL) | 1500 | 96 (81) ^d |
| 6 | 1.0 | AcOH (0.25 mL) | 1500 | 87 |
| 7 | 1.0 | AcOH (0.5 mL) | 1500 | 90 |
| 8 | 1.0 | AcOH (1.0 mL) | 1500 | 98 |
| 9 | 2.0 | AcOH (1.0 mL) | 1500 | 97 |
| 10 | 1.0 | AcOH (1.0 mL) | 0 | 5 |
| 11 | 1.0 | AcOH (1.0 mL) | 500 | 8 |
| 12 | 1.0 | AcOH (1.0 mL) | 1000 | 16 |

^aReactions shown in A were performed a 1.0 mmol scale with 37% hydrochloric acid (1.0 mL = 12 mmol). ^bRevolutions per minute. ^cYield determined by GC with *n*-decane as internal standard. ^dIsolated yield on a 100 mmol scale; volatile product.

Given that 1-methyl cyclohexene is a rather reactive substrate we continued our study with styrene which was shown to react very sluggishly with hydrochloric acid under non-optimized conditions (Scheme 1C).²³ We were pleased to see that the combination of acetic acid and hydrochloric acid significantly increased the reaction rate especially under vigorous stirring (entries 1, 2 and 5, Table 2). Interestingly, the reaction works better on larger scale, independent if the reaction was stirred with a stirring bar (compare entries 2 and 3) or with an overhead stirrer (entries 6 and 7). We also tested several other carboxylic acids and found that dichloroacetic acid and trifluoroacetic acid are also efficient additives, however these acids are significantly more expensive than acetic acid and therefore were no longer pursued in our studies (See figure S9 in the supporting information (SI)).

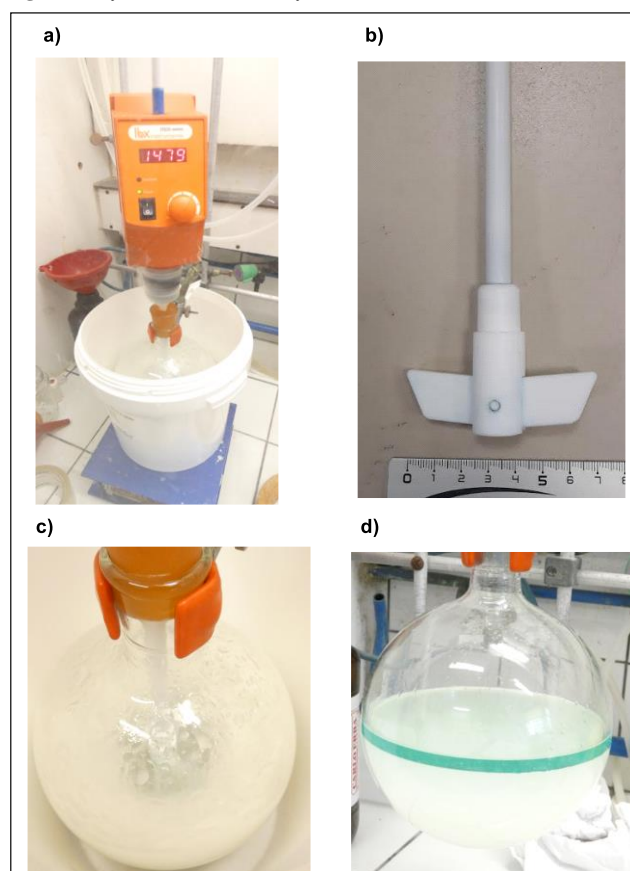
Table 2: Optimization of reaction conditions,^a

| entry | scale (mmol) | rpm ^b | conv (3) (%) ^c |
|----------------|--------------|------------------|------------------------------------|
| 1 | 1 | 0 | 7 |
| 2 | 1 | 500 | 36 |
| 3 | 100 | 500 | 85 |
| 4 | 1 | 1000 | 80 |
| 5 | 1 | 1500 | 87 |
| 6 ^d | 1 | 1500 | 44, 46, 48 ^e |
| 7 ^d | 1000 | 1500 | 81 |

^aReactions shown were performed with 37% hydrochloric acid (1.0 mL = 12 mmol). ^bRevolutions per minute. ^cConversion determined by ¹H-NMR. ^dReactions carried out with only 0.5 mL / mmol hydrochloric acid and acetic acid. ^eConversion of three independently run reactions, demonstrating that the reproducibility of the reaction is correct.

Figure 1 illustrates the reaction of styrene on large scale. Styrene (1 mole), 500 mL hydrochloric acid (37%) and 500 mL acetic acid were placed in a 2 L round bottom flask and stirred at 1500 rpm with a digital overhead stirrer (Ibx instruments, OS20, Figure 1a) equipped with a PTFE stirrer blade (see Figure 1b). In fact, styrene is soluble in acetic acid but is only partially soluble in the acetic acid-hydrochloric acid mixture. Hence, upon stirring an unstable emulsion is produced (figure 1c) which separates into two phases once stirring is stopped (Figure 1d). The reaction shows 81% conversion after 1 h at rt (Table 2, entry 7), however it takes 10 h at rt for the complete consumption of styrene. Standard work-up of the reaction afforded the desired product **4** in 96% yield and 98% purity. It is noteworthy, that hydrochlorination reactions with HCl gas solutions in acetic acid were studied previously by Fahey.²⁵ However, a 93:7 mixture of chloride **4** and 1-phenylethyl acetate was obtained. In this report, the acetate content was determined to be less than 2% as determined by ¹H-NMR analysis.

Figure 1: Hydrochlorination of styrene on a 1-mole scale.

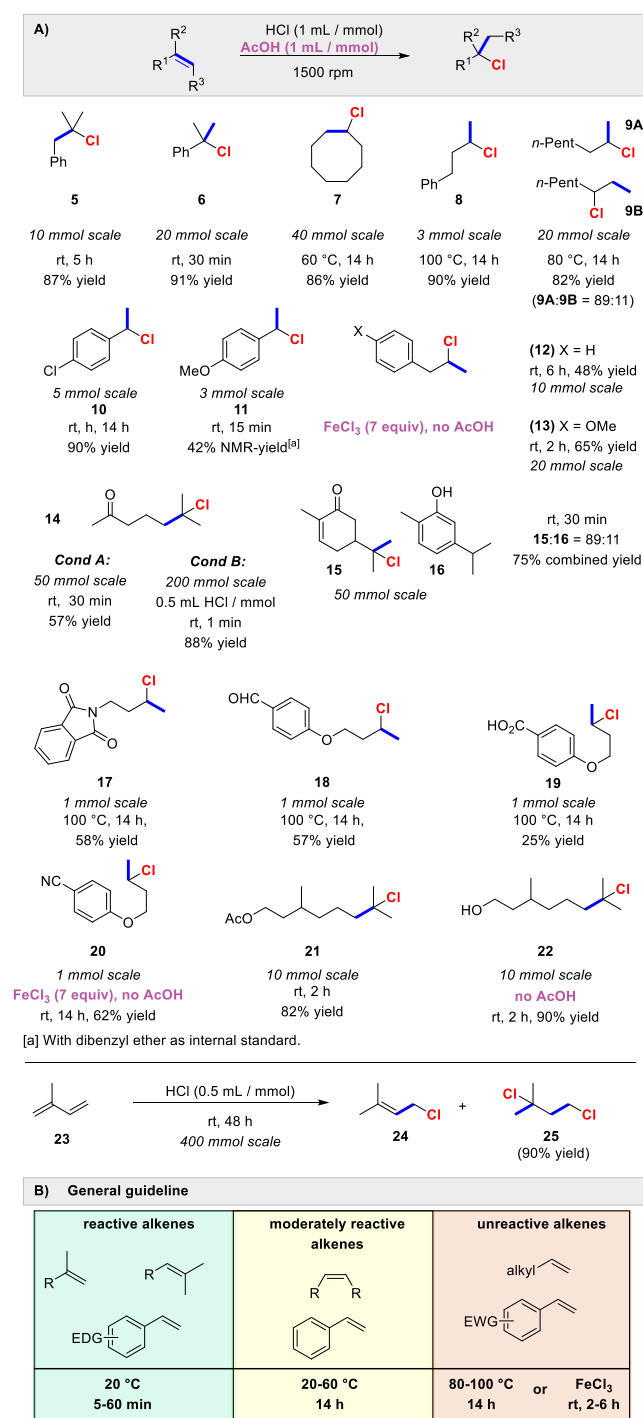


^aReaction set-up on a 1-mol scale; bucket was added in case the 2 L round bottom glass flask should break. ^bDimensions of PTFE stirrer blade used (units in cm). ^cUnstable emulsion formed while stirring at 1500 rpm. ^dPhases separate within minutes once stirring is stopped.

Encouraged by the notable acceleration of the reaction by vigorous stirring and acetic acid, we investigated the hydrochlorination of various other alkenes (Figure 3A). The hydrochlorination of 1,1-disubstituted alkenes proceeded smoothly, resulting in high yields of tertiary chlorides **5** and **6**. As expected cyclooctene required elevated reaction temperatures (product **7**), whereas terminal non-activated alkene required relatively harsh conditions (**8** and **9**). Chloro substituted styrene afforded the desired product **10** in 90% yield. In contrast, *para*-methoxy

styrene gave only a gel like product. Dilution of the styrene in dichloromethane and only 5 equivalents of hydrochloric afforded **11** in 42% NMR-yield accompanied with what appears to be a oligo- or polymer side-product. Allylbenzene and 4-allyl anisole gave pure **12** and **13** with anhydrous FeCl_3 as additive²⁶ and subsequent distillation. We noticed that for allylbenzenes the regioselectivity was higher in the presence of FeCl_3 instead of AcOH. A plausible explanation for the high regioselectivity is given in the SI (Figure S10 and discussion). Interestingly, ketones tolerate the relatively harsh reaction conditions, and the corresponding chloride **14** was isolated in 57% yield after distillation (Condition A). Consistent with previous observations,^{11,23} carvone gave an 89:11 mixture of the desired product **15** and **16**. Phthalimide- and aldehyde-substituted alkenes gave the corresponding products **17** and **18** respectively. Under standard conditions, hydrochlorination of a benzonitrile was accompanied by hydrolysis of the nitrile, resulting in a low yield of carboxylic acid **19**. To our delight, iron trichloride emerged as a beneficial additive, preserving the integrity of the nitrile group and enabling the isolation of the targeted product **20** with a satisfactory yield of 62%. Interestingly, chlorides **8**, **17**, **18**, **19** and **20** were all isolated with high regioisomeric purity (typically > 95:5 of Cl substitution in the 2-position). Most likely, the neighboring aryl substituent or heteroatoms stabilized the secondary cation generated *in situ* and thus prevented hydride migrations. In contrast, hydrochlorination of 1-octene gave an inseparable 81:19 mixture of 2-chlorooctane (**9A**) and 3-chlorooctane (**9B**). Based on Paquin's report¹⁴ we confirmed that the transformation of octan-1-ol into the corresponding acetate is a very fast process, resulting in 95% conversion in less than 20 minutes under standard hydrochlorination conditions. Therefore, citronellol was expected to yield the corresponding acetate **21** upon treatment with HCl/AcOH. From previous experiments with alkene **1** (table 1), we knew that the hydrochlorination of trisubstituted alkenes is relatively facile and can also be carried out in the absence of acetic acid. Thus, stirring the reaction for two hours with only hydrochloric acid gave the hydrochlorinated citronellol **22** in 90% yield. This finding demonstrates that our procedure does not require protection of the primary alcohols when reactive alkenes are submitted to hydrochlorination. Monitoring the progress of the hydrochlorination of isoprene (**23**) by ¹H-NMR analysis showed its complete consumption within 30 minutes at rt, yielding a mixture of prenyl chloride **24** and dichloride **25** in a 72:28 ratio. Extending the reaction time to 48 hours led to complete conversion of **24** to give **25** in 90% yield. In this particular case, it is crucial to avoid carboxylic acid or metal halide additives as they lead to a less clean reaction profile.

Figure 2. Substrate scope



The results obtained can be summarized as follows: a) trisubstituted alkenes and styrenes (e.g. **1**) are readily hydrochlorinated with hydrochloric acid at rt with or without acetic acid; b) monosubstituted alkenes (e.g. styrene) and disubstituted alkenes (e.g. cyclooctene) require longer reaction times and in some cases higher reaction temperatures; c) addition of FeCl_3 , allows for the hydrochlorination of unactivated terminal alkenes at rt.²⁷ A general guideline for the choice of reaction conditions is depicted in Figure 3B.

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pointed out that the stirring rate is very likely dependent on the character of the mixture (biphasic or homogenous) which depends on the polarity of the substrate. Hence, we tested all the substrates leading to the described products and found for most cases biphasic mixtures with 37% hydrochloric acid and acetic acid mixtures (1 mL each per mmol of substrate). However, some of the most polar alkenes used in this study: 6-methyl-5-hepten-2-one (water solubility 3.02 g/L)²⁸, carvone (1.3 g/L)²⁹ and citronellol (water solubility 307 mg/L)²⁹ gave homogenous solutions in HCl / AcOH mixtures and we observed that conversions were independent of the stirring rates. In fact, 6-methyl-5-hepten-2-one reacted so fast that even with reduced amounts of HCl (37%, 0.5 mL / mmol) and only 200 rpm the reaction was finished in less than 1 minute despite the biphasic nature of the reaction. To test the scalability thereof, we also tested the reaction on 200 mmol of substrate instead of 1 mmol and found 100% conversion under identical conditions and 88% isolated yield (Figure 2, condition B). Hence, the acceleration through higher stirring rates appears only to be necessary for non-polar substrates.

In conclusion, we report a method for the hydrochlorination of alkenes which relies on common 37% hydrochloric acid. The hydrochlorination of both internal and terminal alkenes is now achievable in reasonable reaction times and the reaction can be easily done on a 1-mole scale. An intriguing aspect is the remarkable tolerance towards many functional groups and the fact that FeCl₃ as an additive even allows the hydrochlorination of substrates containing acid-sensitive nitrile. We anticipate that this method will be widely utilized for the synthesis of secondary and tertiary alkyl chlorides.

ASSOCIATED CONTENT

Data Availability statement

The data underlying this study are available in the published article and its Supporting Information.

Conflict of interest

The research described herein is part of a patent application which was submitted april 18th 2023 (application number EP23305585.4).

Supporting Information

Optimization reactions, experimental procedures and characterization data (¹H NMR, ¹³C NMR, GC-traces). The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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