A Novel One-Pot Conversion of Allyl Alcohols into Primary Allyl Halides Mediated by Acetyl Halide

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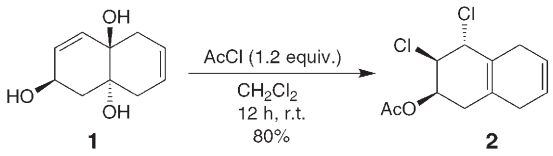
A new and simple method for the synthesis of the primary allyl chlorides and bromides **9**–**16** from the secondary or tertiary allyl alcohols **3**–**8** and acyl halide was developed (*Scheme 2*, *Table 1*). Non-commercially available secondary and tertiary allyl alcohols were synthesized from the related ketones and aldehydes *via* the addition of vinylmagnesium chloride. Mechanistic studies indicate that the alcohols were first acetylated by the acetyl halide and then protonated prior to substitution by the halide, Cl^- or Br^-, *via* an S_N2' reaction, to yield the primary halides (*Scheme 5*).

Introduction. – The conversion of alcohols to alkyl halides is a fundamental transformation in organic synthesis. The utility of alkyl halides in synthesis [1] has stimulated numerous preparations [2]. The general synthesis of alkyl halides employs the treatment of alcohols with a variety of chlorinating agents [3] such as HCl, $SOCl_2$, PCl_3, *etc.*, and many others based on triphenylphosphine [4], in combination with CCl_4, R_2SeCl_2 [2b], and Cl_3CCONH_2 [5]. Alkyl chlorides have also been synthesized by using reagents such as $TiCl_4$ [6] and chlorodimethylsilane/benzil (=1,2-diphenylethane-1,2-dione) in combination with $InCl_3$ [7].

New chlorinating reagents continue to emerge, *e.g.*, [chloro(phenylthio)methylene]dimethylammonium chloride (CPMA), which is used in a mild and selective chlorination for primary alcohols [8]. In addition, some reagent combinations have been used in the course of the stereoselective ring-opening reactions of allylic epoxides and the formation of haloconduritols by S_N2'-type substitution [9]. To the best of our knowledge, although the introduction of a Cl-atom into an epoxide molecule by using acetyl chloride is known, the introduction of two Cl-atoms into a diol by a tandem reaction is novel. We have recently reported on the chlorination of the tertiary allyl alcohol **1** with AcCl *via* a tandem S_N2' reaction (→**2**; *Scheme 1*) [10].

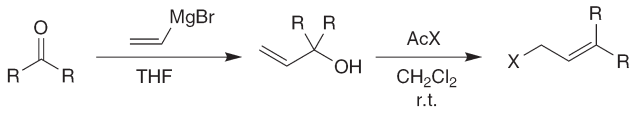
Scheme 1



The present method is an alternative protocol, which enables the introduction of Cl-atoms into similar systems, *i.e.*, into tertiary allyl alcohols. The method is applicable to a

large number of alcohols and represents a valuable protocol for synthesizing allyl chlorides and bromides. The diverse secondary and tertiary allyl alcohols are readily accessible from the related ketones *via* addition of vinylmagnesium bromide (*Scheme 2*).

Scheme 2



Results and Discussion. – The conversion of the allyl alcohols to allyl chlorides is remarkably selective by using AcCl in CH_2Cl_2. Thus, the secondary allyl(phenyl) alcohol **8** and the tertiary allyl alcohols **3**–**7** give with AcCl or AcBr only the rearranged allyl chlorides or bromides **9**–**16** (*Table 1*), whereas application of the same procedure to primary and secondary allyl alcohols, *i.e.*, to **17** and **18**, affords esters, *i.e.*, **19** and **20** without rearrangement to the allyl halide (*Table 2*). In a recent paper [8], a similar system, $PrCH{=}CHCH_2OH$, has been converted to the corresponding alkyl halide by employing CPMA, in contrast to our result with the primary alcohol **17** (*Table 2*, *Entry 1*). The reaction of CPMA with a primary alcohol converts the OH group into a very good leaving group which can be substituted easily by Cl^-. In our case, **17** forms an ester **19** with AcCl (*Table 2*, *Entry 1*). Apparently, the ester group of **19** does not increase the electrophilicity sufficiently to enable attack by Cl^-; therefore, no alkyl halide is formed.

Table 1. *Reaction of Secondary and Tertiary Allyl Alcohols with Acetyl Chloride or Acetyl Bromide*

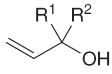
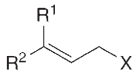
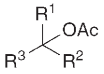
Entry		Time [h]		Yield [%]
1	**3** R^1, $R^2 = Me$	1	**9** R^1, $R^2 = Me$, $X = Cl$	95
2	**4** R^1, $R^2 = Pr$	36	**10** R^1, $R^2 = Pr$, $X = Cl$	87
3	**5** R^1, $R^2 = Ph$	12	**11** R^1, $R^2 = Ph$, $X = Cl$	90
4	**6** $R^1 = Me$, $R^2 = Ph$	12	**12** $R^1 = Me$, $R^2 = Ph$, $X = Cl$	90
5	**7** $R^1 - R^2 = (CH_2)_5$	12	**13** $R^1 - R^2 = (CH_2)_5$, $X = Cl$	80
6	**8** $R^1 = H$, $R^2 = Ph$	12	**14** $R^1 = H$, $R^2 = Ph$, $X = Cl$	80
7	**3** R^1, $R^2 = Me$	1	**15** R^1, $R^2 = Me$, $X = Br$	80
8	**5** R^1, $R^2 = Ph$	12	**16** R^1, $R^2 = Ph$, $X = Br$	95

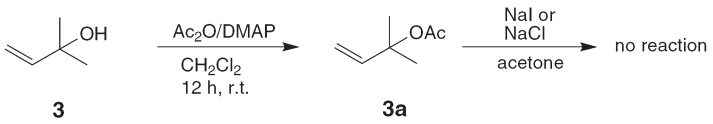
Table 2. *Reaction of Primary and Secondary Allyl Alcohols and of Tertiary Alcohols with Acetyl Chloride*

Entry		Time [h]		Yield [%]
1	**17** R^1, $R^2 = H$, $R^3 = CH_2{=}CH$	24	**19** R^1, $R^2 = H$, $R^3 = CH_2{=}CH$	90
2	**18** $R^1 = H$, $R^2 = CH_2{=}CH$, $R^3 = Pr$	24	**20** $R^1 = H$, $R^2 = CH_2{=}CH$, $R^3 = Pr$	70
3	**21** R^1, R^2, $R^3 = Me$	24	**23** R^1, R^2, $R^3 = Me$	98
4	**22** R^1, $R^2 = Me$, $R^3 = Et$	24	**24** R^1, $R^2 = Me$, $R^3 = Et$	95

The treatment of the tertiary alcohols **21** and **22** with AcCl also gives no alkyl halides but only the esters **23** and **24** (*Table 2*). From these experiments, it can be concluded that the presence of a tertiary allyl alcohol moiety is essential for the successful rearrangement under the chosen conditions.

A mechanistic analysis indicates that the reaction proceeds *via* an S_N2' process catalyzed by acid. We hypothesized that this reaction could take place *via* esterification followed by nucleophilic attack at the $=CH_2$ group under acidic condition. To test the requirement of acid in the transformation of **3** to **9** under our conditions, ester **3a** was synthesized from **3** with *N*,*N*-dimethylpyridin-4-amine (DMAP)/Ac_2O (*Scheme 3*). When **3a** was treated with NaI or NaCl, no reaction was observed, implying that the S_N2' reaction requires acid, which is often present in samples of AcX because of its moisture sensitivity. In addition, HCl is also produced in the reaction of an alcohol with AcCl. Supportive evidence for the need of traces of acid was obtained by performing the following tentative halogenation reactions. If 1 equiv. of **3** was exposed to 0.2 equiv. of Et_3N and 0.2 equiv. of AcCl, no rearranged halide **9** or ester **3a** was formed. Similarly, 1 equiv. of **3** in the presence of 1 equiv. of 2,6-lutidine (=2,6-dimethylpyridine) and 1 equiv. of AcCl did not afford ester **3a** or allyl halide **9**. Probably Et_3N and 2,6-lutidine reacted with AcCl to form an acetyl-Et_3N or acetyl-2,6-lutidine intermediate. It is known that such a type of intermediate reacts sluggishly with sterically crowded alcohols to form esters [12]. The results obtained under HCl-free conditions by using Et_3N or 2,6-lutidine indicate that the presence of HCl in small amounts is necessary to promote the halogenation under our reaction conditions.

Scheme 3

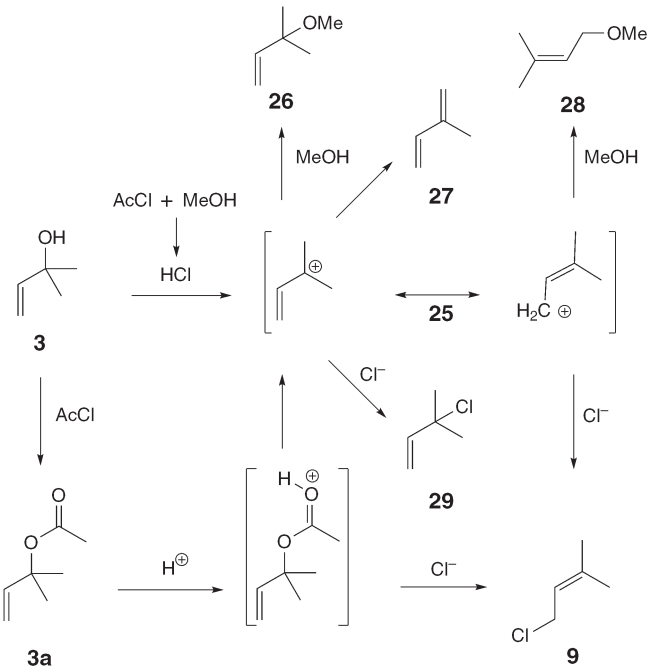


Formation of the allyl chloride could potentially occur directly from the allyl alcohol in the presence of HX, the synthesis of **9** from **3** by using concentrated HCl solution being known [11]. Consequently, allyl alcohol **3** was treated with dry HCl in Et_2O. The crude NMR showed the desired allyl halide accompanied by significant amounts of by-products, which are not observed under our standard conditions, suggesting that the reaction with AcCl involves the esters and does not occur directly from the protonated alcohol *via* S_N2' displacement.

The possibility of an S_N1 mechanism was also probed. Treatment of **3** and AcCl with MeOH (1 to 10 equiv.) would first liberate HCl, which would protonate the OH group of **3** forming a good leaving group and subsequently a tertiary carbocation **25** stabilized by inductive and mesomeric effects (*Scheme 4*). As expected, AcCl could also give ester **3a** under the same conditions. It is known that the hydrolysis of esters of carboxylic acids and tertiary alcohols under acidic conditions takes place according to the $A_{AL}1$ mechanism yielding a stable carbocation. Thus, if the $A_{AL}1$-type of cleavage occurred in **3a**, the further reaction to **9** would also occur *via* **25**. Either formed by ester cleavage or by a simple S_N1 reaction, the carbocation **25** should then react with chloride and MeOH to give **9**, **26**, **28**, and **29**. Another possibility would be that carbocation **25**

undergoes an elimination reaction to product **27**. Excess of MeOH would be in competition with Cl^- as nucleophile to react with the carbocation to give methyl ethers **26** and **28** in case of an S_N1-type reaction. However, NMR studies during the reaction of **3** with AcCl in MeOH revealed only the formation of allyl halide **9**.

Scheme 4

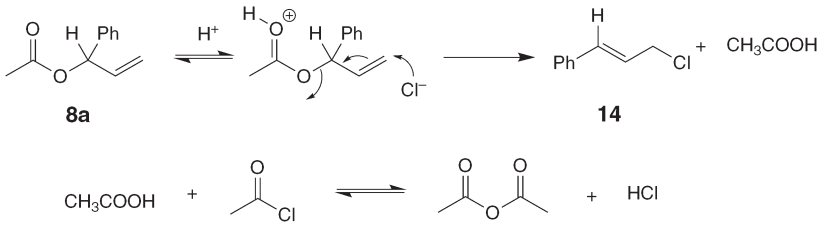


Further evidence that this reaction does not occur *via* an S_N mechanism is that the tertiary alcohols **21** and **22**, on treatment with AcCl, did not yield the related chlorides but esters (*Table 2*). If the reaction would proceeded *via* an S_N1 mechanism before esterification or after protonation of the ester O-atom, this would result in a highly stable carbocation (according to the $A_{AL}1$ mechanism) which is prone to nucleophilic attack by Cl^- ions.

We carried out another experiment with ester **8a** (*Scheme 5*), which was synthesized separately for a better understanding of this reaction. Thus, a solution of **8a** in $CDCl_3$ was treated with AcCl in the NMR tube and the reaction monitored by taking ^{1}H-NMR spectra at intervals. As the halogenation reaction proceed, a Me signal increased at δ(H) 2.16, which corresponds to Ac_2O. The ^{13}C-NMR spectra also established the formation of Ac_2O (δ(C) 24.0 (Me) and 168.4 (C=O)). This was confirmed by the addition of Ac_2O to the mixture, which resulted in an increase of the signals at δ(H) 2.16 and δ(C) 24.0 and 168.4. We believe that AcCl contains traces of HCl, which protonates the carbonyl O-atom of **8a**, thus making the acetyl unit a good leaving group. Nucleophilic attack by Cl^- in an S_N2' fashion would lead to **14** and

AcOH. Subsequently, the formed AcOH would plausibly form Ac_2O with AcCl (*Scheme 5*).

Scheme 5



The above observations and those of our previous study [10] confirm that the halogenation reaction of the tertiary allyl alcohols of our work proceeds only by the S_N2' mechanism *via* the corresponding acetates.

Conclusion. – We described an efficent and convenient one-pot synthesis of primary allyl chlorides and bromides from allyl alcohols by using an acyl halide. The reaction is selective for tertiary allyl alcohols and for a secondary allyl (phenyl) alcohol. Mechanistic studies indicate the intermediate formation of allyl esters that are protonated and subsequently displaced by chloride through an S_N2' displacement. This method has the potential to be widely used in organic synthesis because of the facile access to halides enabling further elaboration.

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Experimental Part

1. *General.* Solvents were purified and dried by standard procedures before use. Column chromatography (CC): Silica gel *60* (70–230 mesh) and *Alox* (neutral Al_2O_3, type III). M.p.: *Büchi-539* melting-point apparatus (in capillary); uncorrected. ^{1}H- and ^{13}C-NMR Spectra: *Varian* spectrometer, at 400 or 100 MHz, in $CDCl_3$; δ in ppm, J in Hz.

2. Grignard *Reaction: General Procedure* [13]. To a soln. of ketone or aldehyde (2 g, 1 equiv.) in THF (40 ml) was added 1M vinylmagnesium bromide (1.2 equiv.) at $-78°$ under Ar. After stirring for 3 h, the soln. was warmed to r.t. The reaction was quenched with ice (15 g), and the mixture was diluted with a sat. NH_4Cl soln. The THF was evaporated, the crude mixture extracted with Et_2O (2×100 ml), and the extract washed with NaCl (2×30 ml), dried ($MgSO_4$), and concentrated: alcohols.

3. *Chlorides: General Procedure.* To a magnetically stirred soln. of alcohol (1 g, 1 equiv.) in CH_2Cl_2 (10 ml) was added AcCl (1.5 equiv.). The mixture was stirred at r.t. After addition of H_2O (50 ml), the org. layer was washed with aq. $NaHCO_3$ soln. (50 ml) and H_2O (50 ml), dried (Na_2SO_4), and concentrated: allyl chlorides.

1-Chloro-3-methylbut-2-ene (**9**) [11]: ^{1}H-NMR (200 MHz): 5.41 (*tsept.*, $J = 8$, 1.4, 1 H); 4.07 (*d*, $J =$ 7.8, 2 H); 1.76 (br. *s*, 3 H); 1.72 (br. *s*, 3 H). ^{13}C-NMR (50 MHz): 141.2; 122.6; 43.1; 27.6; 19.6.

4-(2-Chloroethylidene)heptane (**10**) [14]: ^{1}H-NMR (400 MHz): 5.23 (*t*, $J = 8$, 1 H); 4.1 (*d*, $J = 8$, 2 H); 2.06 (*t*, $J = 7.7$, 2 H); 2.02 (*t*, $J = 8$, 2 H); 1.42 (*dsept.*, $J = 7.3$, 2.9, 4 H); 0.90 (*t*, $J = 2.9$, 3 H); 0.86 (*t*, $J = 2.9$, 3 H). ^{13}C-NMR (100 MHz): 146.8; 120.7; 41.2; 39.0; 32.3; 21.8; 21.1; 14.3; 14.0.

1,1′-(3-Chloroprop-1-en-1-ylidene)bis[benzene] (**11**) [15]: ^{1}H-NMR (400 MHz): 7.45–7.24 (*m*, 10 H); 6.28–6.24 (*d*, *J* = 8, 1 H); 4.16 (*d*, *J* = 8, 2 H). ^{13}C-NMR (100 MHz): 146.4; 141.4; 138.5; 129.9; 128.6; 128.5; 128.3; 128.1; 128.0; 123.9; 42.9.

*[(1*E*/*Z*)-3-Chloro-1-methylprop-1-en-1-yl]benzene* (**12**) [16]: ^{1}H-NMR (400 MHz; (*E*)/(*Z*) 4:1; determined by NOE): (*E*)-**10**: 7.44–7.25 (*m*, 5 H); 6.01 (*tq*, *J* = 7.7, 1.1, 1 H); 4.29 (*d*, *J* = 7.7, 2 H); 2.16 (*d*, *J* = 1.1, 3 H); (*Z*)-**10**: 7.44–7.25 (*m*, 5 H); 5.75 (*tq*, *J* = 8.2, 1.1, 1 H); 4.01 (*d*, *J* = 8.2, 2 H); 2.16 (*d*, *J* = 1.1, 3 H). ^{13}C-NMR (100 MHz) (*E*)-**10**: 142.5; 141.1; 128.6; 128.0; 126.2; 123.0; 41.3; 16.0; (*Z*)-**10**: 142.5; 140.0; 128.6; 127.8; 127.7; 123.0; 42.7; 25.7.

(2-Chloroethylidene)cyclohexane (**13**) [17]: ^{1}H-NMR (400 MHz): 5.39 (*td*, *J* = 8.1, 1.1, 1 H); 4.10 (*d*, *J* = 8.1, 2 H); 2.21 (br. *s*, 2 H); 2.12 (br. *s*, 2 H); 1.56 (br. *s*, 6 H). ^{13}C-NMR (100 MHz) : 147.4; 117.4; 40.7; 37.1; 28.9; 28.5; 27.9; 26.8.

*[(1*E*)-3-Chloroprop-1-en-1-yl]benzene* (**14**) [18]: ^{1}H-NMR (400 MHz): 7.43–7.28 (*m*, 5 H); 6.67 (*d*, *J* = 15.3, 1 H); 6.34 (*dt*, *J* = 15.3, 7.3, 1 H); 4.26 (*d*, *J* = 7.3, 2 H). ^{13}C-NMR (100 MHz): 136.1; 134.4; 128.9; 128.5; 126.9; 125.1; 45.7.

1-Bromo-3-methylbut-2-ene (**15**) [11]: ^{1}H-NMR (400 MHz): 5.51 (*tq*, *J* = 2.6, 1.1, 1 H); 3.99 (*d*, *J* = 8.4, 2 H); 1.77 (*s*, 3 H); 1.72 (*s*, 3 H). ^{13}C-NMR (100 MHz): 140.3; 121.0; 29.9; 26.0; 17.8.

1,1′-(3-Bromoprop-1-en-1-ylidene)bis[benzene] (**16**) [15]: ^{1}H-NMR (400 MHz): 7.49–7.23 (*m*, 10 H); 6.34 (*t*, *J* = 8.4, 1 H); 4.06 (*d*, *J* = 8.4, 2 H). ^{13}C-NMR (100 MHz): 146.4; 141.4; 138.4; 129.7; 128.6; 128.4; 128.3; 128.1; 127.9; 123.9; 31.4.

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