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A New Preparative Route to Organic Halides from Alcohols via the Reduction of Polyhalomethanes

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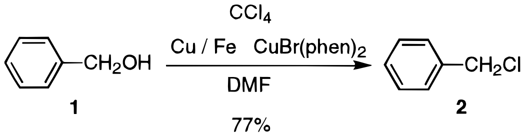
Many methods of preparation of alkyl halides from alcohols are known. The most commonly used preparative routes are the reactions of alcohols either with hydracids or with phosphorus halides.[1a−c] We have found a convenient alternative which involves polyhalomethanes as the source of halogen in the presence of a redox system. This process was first observed during the electroreduction of CCl_4 and $BrCCl_3$ in *N*,*N*-dimethylformamide (DMF) in the presence of various functional groups including aldehydes and alcohols. The electrolyses were conducted in an undivided cell and in the presence of a stainless-steel cathode and a sacrificial anode. The conversion of alcohols into the corresponding halides occurred mainly with copper as the sacrificial anode, and the reaction was found to be even more efficient with some 1,10-phenanthroline (phen) added to the reaction mixture. We also noticed an overconsumption of the anode (based on the charge passed) along with an unexpected consumption of the cathode. We have found that the reaction does not require the supply of electricity and can occur in a purely chemical mode. Indeed the reaction can be conducted in a round-bottom flask using either piece, or a powder of copper and iron and small amounts of $Cu^I(phen)_2$.

We report in this paper the details of a simple and efficient method to prepare primary alkyl halides from primary alcohols and β-halo-α,β-unsaturated ketones from β-diketones. We also discuss two possible reaction mechanisms, which can be discriminated according to the nature of the solvent. The conversion of aldehydes into *gem*-dihalides is currently under study, and the results will be reported shortly.

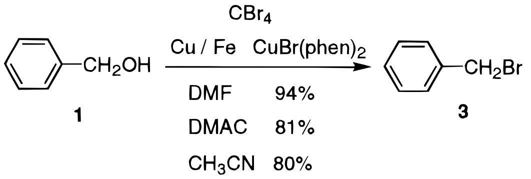
Results

The best reaction conditions were determined using benzyl alcohol or 1-decanol as model systems. Thus the preparation of benzyl chloride was conducted in DMF using CCl_4 as halogenating agent (eq 1). Under the standard reaction conditions (for 20 mmol of $PhCH_2OH$: CuBr (0.5 mmol), 1,10-phenanthroline (1 mmol), copper powder (30 mmol), iron powder (50 mmol), 2 equiv of CCl_4 (40 mmol), 3 h at room temperature), benzyl chloride was produced in 77% isolated yield. With CBr_4, benzyl alcohol was converted into benzyl bromide nearly quantitatively (1.5 h at room temperature). With $BrCCl_3$ a 4:1 mixture of benzyl chloride and bromide was obtained in 80% overall yield (1.5 h at room temperature). Apart from the efficiency of the process, two other features are worth mentioning, i.e. the acidic medium obtained at the end of the reaction and the evolution of carbon monoxide.



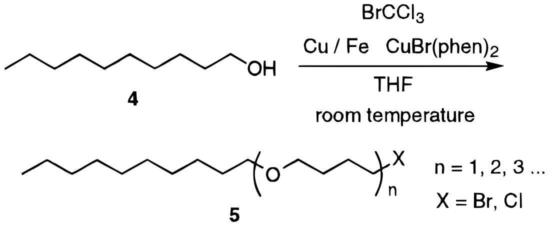
(1)

Other solvents were tested using benzyl alcohol and CBr_4 at room temperature. As summarized in eq 2, the preparation of benzyl bromide can be carried out in *N*,*N*-dimethylacetamide (DMAC) or in acetonitrile (CH_3CN), though with a slower rate and a slightly lower efficiency than in DMF.



(2)

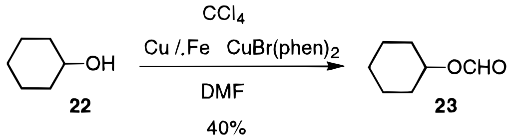
We also used tetrahydrofuran (THF) as solvent with 1-decanol and obtained products derived from the opening of THF (eq 3).



(3)

To test the generality of the procedure to prepare alkyl halides, we carried out the reaction using several alcohols. The results are given in Table 1.

It can be seen that the procedure is applicable to primary alcohols, whereas the main or only products formed from secondary alcohols (Table 1, entries 7 and 8) or cyclohexanol (eq 4) were the corresponding alkyl formates.



(4)

Thus in a mixed primary and secondary diol, only the primary group is converted into the halide while the secondary group is protected in the form of the corresponding formate (Table 1, entries 13 and 14) as already observed by Boeckman et al.[2] A higher yield of the halo formate was obtained at higher reaction temperature (e.g. 100 °C, Table 1, entry 14).

The sole secondary alcohol which gave the corresponding chloride (30%) with CCl_4 or bromide (85%) with CBr_4 is ethyl lactate (Table 1, entries 9 and 10). We expected a stereospecific reaction with the commercially available (*S*)-ethyl lactate, but we only obtained the racemic bromide or chloride, in keeping with reaction mechanisms discussed below.

Attempts to convert allylic alcohols into allylic halides were unsuccessful. The main product obtained from

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[1] (a) For a list of reagents with references, see: Larock, R. C. *Comprehensive Organic Transformations*, VCH: New York, 1989, p 353. (b) Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964. (c) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801.

[2] Boeckman Jr., R. K.; Ganem, B. *Tetrahedron Lett.* **1974**, *11*, 913.

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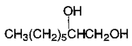
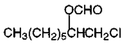
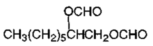
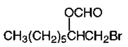
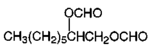
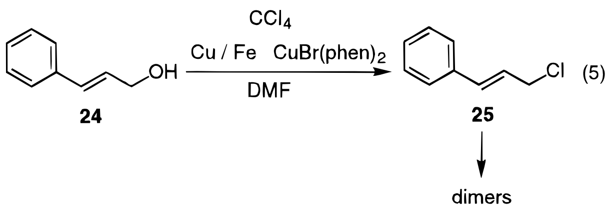
Table 1. Conversion of Alkanols into Alkyl Halides[a]

entry	ROH	CX_4	Products		Yield (%)[b]
1	$C_6H_5CH_2OH$ **1**	CCl_4	$C_6H_5CH_2Cl$ **2**		77
2		CBr_4	$C_6H_5CH_2Br$ **3**		94
3		$BrCCl_3$	$C_6H_5CH_2Cl$ **2** (80)	$C_6H_5CH_2Br$ **3** (20)	80
4	$CH_3(CH_2)_8CH_2OH$ **4**	CCl_4	$CH_3(CH_2)_8CH_2Cl$ **6**		83
5		CBr_4	$CH_3(CH_2)_8CH_2Br$ **7** (85)	$CH_3(CH_2)_8CH_2OCHO$ **8** (15)	95
6		$BrCCl_3$	$CH_3(CH_2)_8CH_2Cl$ **6** (80)	$CH_3(CH_2)_8CH_2Br$ **7** (20)	90
7	$CH_3(CH_2)_5CH(CH_3)OH$ **9**	CCl_4	$CH_3(CH_2)_5CH(CH_3)OCHO$ **10**		70
8		CBr_4	$CH_3(CH_2)_5CH(CH_3)Br$ **11** (10)	$CH_3(CH_2)_5CH(CH_3)OCHO$ **10** (90)	39
9	(*S*) $CH_3CH(OH)CO_2C_2H_5$ **12**	CCl_4	$CH_3CH(Cl)CO_2C_2H_5$ **13**		30[c]
10		CBr_4	$CH_3CH(Br)CO_2C_2H_5$ **14**		85[c]
11	$HOH_2C{-}C{\equiv}C{-}CH_2OH$ **15**	CCl_4	$ClCH_2{-}C{\equiv}C{-}CH_2Cl$ **16**		30
12		CBr_4	$BrCH_2{-}C{\equiv}C{-}CH_2Br$ **17**		74
13	 $CH_3(CH_2)_5\overset{OH}{\overset{\vert}{C}}HCH_2OH$ **18**	CCl_4	 $CH_3(CH_2)_5\overset{OCHO}{\overset{\vert}{C}}HCH_2Cl$ **19** (60)	 $CH_3(CH_2)_5\overset{OCHO}{\overset{\vert}{C}}HCH_2OCHO$ **20** (40)	75
14		CBr_4	 $CH_3(CH_2)_5\overset{OCHO}{\overset{\vert}{C}}HCH_2Br$ **21** (70)	 $CH_3(CH_2)_5\overset{OCHO}{\overset{\vert}{C}}HCH_2OCHO$ **20** (30)	88[d]

[a] Alcohol: 0.3 mol dm^{-3}, CX_4: 0.6 mol dm^{-3}, DMF: 70 ml, CuBr: 7 10^{-3} mol dm^{-3}, phen: 14 10^{-3} mol dm^{-3}, Cu (metal): 0.43 mol dm^{-3}, Fe (metal): 0.76 mol dm^{-3}, room temperature, 0.5 to 3 h. [b] Isolated yield. [c] Racemic bromide or chloride. [d] Reaction at 100°C, 24 h.

cinnamyl alcohol was the dimer, likely formed via the intermediate cinnamyl halide (eq 5).



On the contrary, an easily isolable dihalide was obtained in good yield from 2-butyne-1,4-diol (Table 1, entries 11 and 12).

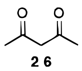
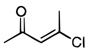
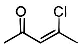
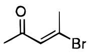
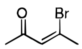
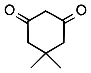
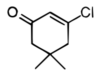
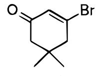
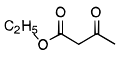
The procedure can also be used to convert β-diketones into β-halo-α,β-unsaturated ketones. The results are summarized in Table 2.

2,4-Pentanedione gave a mixture of *E* and *Z* stereoisomeric β-halo enones (in 3:1 *E*:*Z* ratio for β-chloro enone, Table 2, entry 1; and 4:1 *E*:*Z* ratio for β-bromo enone, Table 2, entry 2). With dimedone the β-halo enone was formed in quite good yields (Table 2, entries 3 and 4). For these two reagents the reaction gave higher yields with CBr_4 than with CCl_4. Attempts to convert ethyl acetoacetate under our standard reaction conditions failed. The halogenation of dimedone conducted in acetonitrile or in DMAC was also unsuccessful.

Discussion

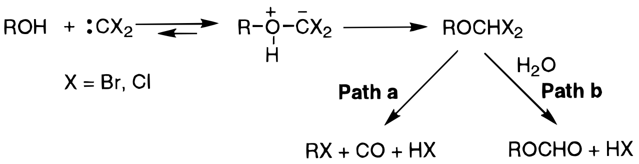
Polyhalomethanes, either haloforms in the presence of a strong base or CCl_4 in an electroreductive process,[3a,b] have already been used for the halogenation of alcohols. The reactions likely proceed according to a mechanism proposed by Tabushi et al.[4] In the presence of a base, the deprotonation of chloro- or bromoform generates dihalocarbenes which in the presence of an olefin lead to dihalocyclopropanes. Tabushi[4] reported in 1971 that dichlorocarbene reacts readily with alcohols to give the corresponding chlorides according to the mechanism depicted in Scheme 1: a formal insertion of CCl_2 into the OH bond of ROH leads to the α,α-dichloro ether which, when R is a primary alkyl group, decomposes either concertedly or via the formation of a carbocation into the corresponding alkyl chloride RCl with the evolution of CO (path a). The formation of alkyl formate from secondary alcohols, though not explained by Tabushi,[4] can also be accounted for by the involvement of a carbene intermediate (Scheme 1, path b). The formation of benzyl chloride by electroreduction of CCl_4 in the presence of benzyl alcohol (Petrosyan's work[3a,b]) or by chemical reduction (our copper/iron system) can also be explained by a carbene route.

Table 2. Preparation of β-Halo-α,β-unsaturated Ketones[a]

Entry	Dicarbonyl compound	CX_4	Products		Yield (%)[b]
1	 **26**	CCl_4	 (*E*) **27**	+  (*Z*) **27**	33
2		CBr_4	 (*E*) **28**	+  (*Z*) **28**	54
3	 **29**	CCl_4	 **30**		86
4		CBr_4	 **31**		95
5	 **32**	CCl_4	-		-
6		CBr_4	-		-

[a] Dicarbonyl compound: 0.3 mol dm^{-3}, CX_4: 0.6 mol dm^{-3}, DMF: 70 ml, CuBr: 7 10^{-3} mol dm^{-3}, phen: 14 10^{-3} mol dm^{-3}, Cu (metal): 0.43 mol dm^{-3}, Fe (metal): 0.76 mol dm^{-3}, room temperature, 2 h. [b] Isolated yield.

Scheme 1



This reaction scheme does not however take into account the possible role of the solvent. We have observed that the reaction is more rapid and more efficient in DMF than in DMAC or acetonitrile,[5] that the evolution of CO is more facile in DMF than in the other solvents, and finally that the halogenation of dimedone was unsuccessful in all solvents used except DMF. We postulated a possible reaction between dihalocarbenes and DMF, and indeed found that the production of CO

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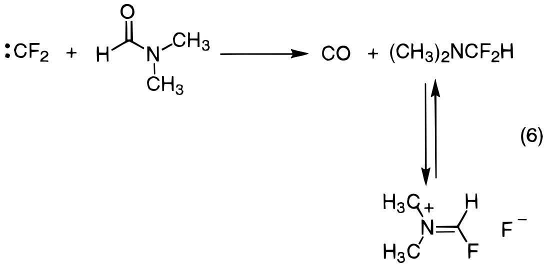
(3) (a) Petrosyan, V. A.; Niyazymbetov, M. E.; Baryshnikova, T. K. *Izv. Akad. Nauk SSSR* **1988**, *1*, 91. (b) Petrosyan, V. A.; Niyazymbetov, M. E. *Russ. Chem. Rev.* **1989**, *58*, 644.

(4) Tabushi, I.; Yoshida, Z. I.; Takahashi, N. *J. Am. Chem. Soc.* **1971**, *93*, 1820.

(5) The solvent effect was tested on benzyl alcohol.

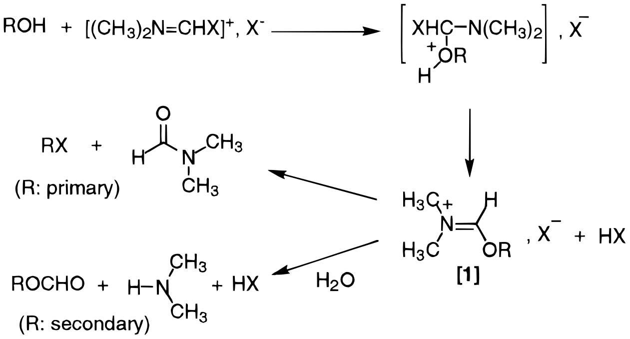
also occurs when CX_4 is reduced chemically in DMF in the absence of alcohol. CO was first characterized by infrared spectroscopy. We also measured the amount of CO evolved using an electroanalytical method as follows: CO was transferred from the reaction flask to an electrochemical cell containing a given amount of an electrochemically generated nickel(0)–bipyridine complex which reacts rapidly with CO to give a well defined $Ni^0(CO)_2$bpy complex, the formation of which is easily monitored using standardized chronoamperometry.[6] The volume of CO was also measured using a measuring test tube connected to the reaction flask.[6] In acetonitrile, or in DMAC, CO was only detected when the alcohol was present.

A similar process has already been reported by Burton and Wiemers[7] for the reduction of CF_2Br_2, CF_2Cl_2, and CF_2BrCl by Zn in DMF. The reaction of the difluorocarbene with DMF leads to CO and (difluoromethyl)dimethylamine in equilibrium with a dimethyliminium fluoride (eq 6).



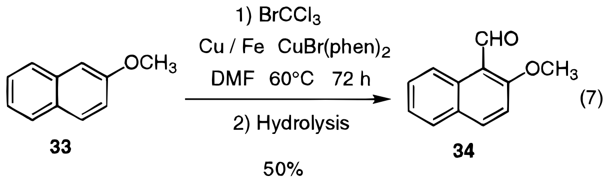
This iminium salt is a typical Vilsmeier reagent which has already been prepared for X = Cl or Br from PCl_5 or $(COX)_2$ and DMF and used to convert primary alcohols into the corresponding halides,[8a,b] β-dicarbonyl compounds into β-halo enones,[9] whereas secondary alkanols or cycloalkanols are converted into alkyl formates[2] according to Scheme 2.

Scheme 2



Thus a common intermediate (**1**) would lead to either the alkyl halide or the alkyl formate. We have indeed observed that even with primary alcohols the formate is the major product if the reaction mixture is hydrolyzed after less than 0.5 h, whereas only the alkyl halide is isolated after a longer reaction time. Hudson[8a] reported that the alkoxydimethyliminium intermediate (**1**) is rapidly formed and can be isolated when R = phenyl. The authors have also shown that the intermediate **1** might racemize at the R group by interaction with DMF.

Evidence consistent with the formation of the Vilsmeier reagent was obtained by performing the formylation of 2-methoxynaphthalene in 50% isolated yield by replacing ROH by the aromatic compound (eq 7).



33 **34**

Conclusion

It is now clear that there are at least two mechanisms leading to the formation of alkyl halides from alcohols or of alkenyl halides from β-dicarbonyl compounds via the reduction of CX_4 according to the nature of the solvent. A typical carbene route (Scheme 1) would be operative in DMAC or acetonitrile but not efficient with β-dicarbonyl compounds, whereas in DMF the dihalocarbene would be rapidly trapped by the solvent leading to the Vilsmeier reagent which can react with alcohols as well as β-dicarbonyl compounds to give the corresponding halides (Scheme 2). It is finally worth noting that the reduction of CX_4 in DMF is a source of CO. Thus *caution* is required when one has to use a solution of CCl_4, CBr_4, or $BrCCl_3$ in DMF in the presence of reducing agents.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a Brucker AC-200 (200 MHz) spectrometer. Mass spectra (electron impact) were obtained on a Finnigan ITD 800 spectrometer coupled to a Varian 3300 chromatograph with a CP Sil-5 capillary column. Gas chromatography was performed on a Varian 3300 chromatograph equipped with a sil-5 CP capillary column. The solvents were used as received.

Preparation of Alkyl Halides. General Procedure. A solution of CX_4 (CCl_4 or CBr_4) diluted in 20 mL of DMF was added to a well-stirred solution of DMF (50 mL) containing CuBr (0.5 mmol), 1,10-phenanthroline monohydrate (1 mmol), copper powder (30 mmol), iron powder (50 mmol), and the alcohol or the dicarbonyl compound (20 mmol) under argon. CAUTION!! The reaction is exothermic and leads to the formation of CO. The temperature was controlled by an ice/water bath. The reaction was monitored by GC and stopped after complete consumption of the alcohol (0.5–3 h). The reaction mixture was then hydrolyzed with hydrochloric acid (1 N). The aqueous layer was extracted with diethyl ether (3 portions of 30 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. Products were isolated by column chromatography (silica gel, 70–230 mesh; eluent pentane). All products are known and gave satisfactory NMR, IR, and mass spectral data.

Analytical Experiments. Electroanalytical experiments were carried out using a three-electrode electrochemical cell under argon. The DMF solution contained 0.1 mol dm^{-3} of Bu_4NBF_4 and 0.1 mol dm^{-3} of a nickel divalent complex made of either $NiCl_2$bpy with 2 bipyridine or $Ni(BF_4)_2bpy_3$. This solution was electrolyzed at constant current of 400 mA to convert the Ni^{II} complex into a Ni^0 complex. In a separate flask connected to the cell, a solution of CX_4 (5 mmol) in DMF (2 mL) was added to the DMF solution (10 mL) containing CuBr (0.07 mmol), 1,10-phenanthroline monohydrate (0.14 mmol), copper powder (4 mmol), and iron powder (7 mmol). The flask was flushed with argon in order to transfer CO into the electrochemical cell. The reaction with CO is very fast and quantitative (eq 8).[10]

In the presence of excess bipyridine the mixture of $Ni^0(CO)_2$bpy and Ni^0bpy_2 is stable. The oxidation of $Ni^0(CO)_2$bpy occurs at

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(6) For more details, see the Experimental Section.

(7) Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014.

(8) (a) Hepburn, D. R.; Hudson, H. R. *J. Chem. Soc., Perkin Trans 1*, **1976**, 754. (b) Fujisawa, T.; Iida, S.; Sato, T. *Chem. Lett.* **1984**, 1173.

(9) Mewshaw, R. E. *Tetrahedron Lett.* **1989**, *30*, 3753.

(10) Oçafrain, M.; Devaud, M.; Troupel, M.; Périchon, J.; Nédélec, J. Y., unpublished work.

$$\mathrm{Nibpy_2 + 2CO \rightarrow Ni(CO)_2bpy + bpy} \qquad (8)$$

−0.2 V/SCE. So, we can measure the disappearance of Ni^0bpy_2 by chronoamperometry at constant potential of −1.2 V/SCE.

We also determined the volume of CO evolved using a measuring test tube. Starting from 5.07×10^{-3} mol (0.5 mL) of $BrCCl_3$ in DMF (12 mL) containing CuBr (0.07 mmol), 1,10-phenanthroline monohydrate (0.14 mmol), copper powder (4 mmol), and iron powder (7 mmol), we obtained 116 mL of CO at 20 °C, which corresponds to 95% yield based on $BrCCl_3$.

Number, name, and registry number provided by the authors (c, commercial; n, new compound): **2**, benzyl chloride [100−44−7], c; **3**, benzyl bromide [100−39−0], c; **6**, 1-chlorodecane [1002−69−3], c; **7**, 1-bromodecane [112−29−8], c; **8**, decyl formate [5451−52−5]; **10**, *sec*-octyl formate [112360−52−8]; **11**, 2-bromooctane, [557−35−7], c; **13**, ethyl 2-chloropropanoate [535−13−7], c; **14**, ethyl 2-bromopropanoate [535−11−5], c; **16**, 1,4-dichlorobut-2-yne [821−10−3]; **17**, 1,4-dibromobut-2-yne [2219−66−1]; **19**, 1-chloro-2-octyl formate, n; **20**, 1,2-octyl diformate, (*Chem. Abstr.* **1952**, *46*, 8146c P); **21**, 1-bromo-2-octyl formate [53067−12−2]; **23**, cyclohexyl formate [4351−54−6]; **27**, (*Z*)-4-chloropent-3-en-2-one [49784−64−7], (*E*) [49784−51−2]; **28**, (*Z*)-4-bromopent-3-en-2-one [80356−21−4], (*E*) [80356−20−3]; **30**, 3-chloro-5,5-dimethylcyclohex-2-en-1-one [17530−69−7]; **31**, 3-bromo-5,5-dimethylcyclohex-2-en-1-one [13271−49−3]; **34**, 2-methoxy-1-naphthalenecarbaldehyde [5392−12−1].

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