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SYNTHESIS OF ALKYL HALIDES UNDER NEUTRAL CONDITIONS

François Munyemana, Anne-Marie Frisque-Hesbain, Alain Devos and Léon Ghosez*
Laboratoire de Chimie Organique de Synthèse
Université Catholique de Louvain, Place L. Pasteur, 1
B-1348 LOUVAIN-LA-NEUVE, BELGIUM

Summary : Primary and secondary alcohols are efficiently converted to the corresponding alkyl halides under neutral conditions.

The readily available[1] tetramethyl-α-halogenoenamines 1 are useful reagents for the conversion of carboxylic acids into the corresponding halides in neutral conditions[2]. Acids containing sensitive functionalities are smoothly converted into halides. When applied to protected aminoacids, the reaction does not lead to racemisation and thus allows the corresponding acid chlorides to be used in peptide synthesis[3].

α–Chloroenamines have been also reported to replace other types of hydroxyl group by chlorine[4]. We report here some preliminary studies on the reaction of α-haloenamines with alcohols.

Scheme 1

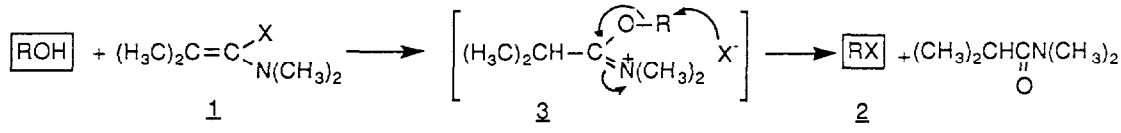
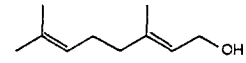
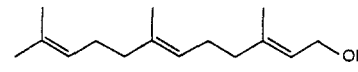
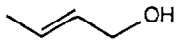


Table 1 : Reaction of primary alcohols with tetramethyl-α-haloenamines at room temperature

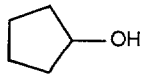
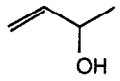
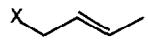
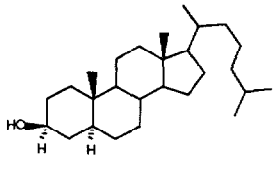
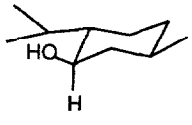
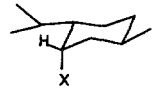
ROH	X	RX yield (%)[a]	ROH	X	RX yield (%)[a]
$CH_3CH_2CH_2CH_2OH$	Cl	97		Cl	95
	Br	96		Br	95
	I	98		I	99
$C_6H_5CH_2OH$	Cl	98		Cl	95
	I	98		I	98
	Cl	99	$HC{\equiv}C{-}CH_2OH$	Cl	99
	Br	98		I	93
	I	99			

[a] Determined by NMR on the crude mixture with an internal standard

Synthesis of chlorides, bromides and iodides

Dichloromethane solutions of alcohols were treated with equimolar amounts of tetramethyl-α-chloro-, bromo- or iodoenamines at room temperature (Scheme 1)[5]. Primary (Table 1) and secondary alcohols (Table 2) were smoothly transformed into the corresponding alkyl halides and N,N-dimethylisobutyramide with no concomitent formation of hydrogen halide. The reaction probably involves the formation of an intermediate iminium salt 3. Attack of halide ion displaces the good amide leaving group. This last step leading to the alkyl-oxygen fission appears to be 100 % SN_2 in character. The reaction occurs with inversion of configuration (Table 2, entries f,g,h). Secondary allylic (Table 2, entry c) and propargyl alcohols (Table 2 entry d) give some rearranged halides. Apparently the amount of rearranged products is time-dependent and mostly occurs after formation of the halide.

Table 2 : Reaction of secondary alcohols with tetramethyl-α-haloenamines at room temperature

Entry	ROH	RX		Remarks
		X	Yield (%)[a]	
a		Cl	80[b]	the crude mixture contains ±6% of cyclopentene
b		Cl	18	+82% of cyclohexene
c		Cl	84	+ rearranged halide 16%
		Br	71	 29%
		I	53	47%
d	$HC{\equiv}CCHOHCH_3$	Cl	98	
		I	94 (after 45 min)	after 4 days, 100% of iodo-allene $ICH{=}C{=}CHCH_3$
e	(±) $CH_3CHOH(CH_2)_5CH_3$	Cl	95	
		Br	96	
		I	98	
f	(+)(S) $CH_3CHOH(CH_2)_5CH_3$	Cl	95[b]	$[\alpha]_D^{20}$ ($CHCl_3$, c=4.5) = -31.5 ~100% inversion
g		Cl	90[b]	reaction occurs with complete inversion ➡ 100% α halide
h		Cl	87	 + 13% olefin
		I	96	+ 4% olefin
				inversion of configuration

[a] Determined by NMR on the crude mixture with an internal standard [b] Isolated pure product

Selectivity

Equimolar amount of butan-1-ol and butan-2-ol were treated with one equivalent of tetramethyl-α–chloroenamine. A 85:15 mixture of primary versus secondary chlorides was obtained. The selectivity was much higher when N,N-diisopropyl-1-chloro-2-methyl propenamine 4, a bulkier chlorinating agent was used. As can be seen in Table 3, reagent 4 allows for the selective conversion of a primary alcohol into the corresponding chloride in the presence of an equimolar amount of a secondary or tertiary alcohol. On the other hand reagent 4 does not discriminate between a primary alcohol and prenyl or benzyl alcohol. This indicates that the selectivities result from the different rates of addition of alcohols to the α-chloroenamine (step1, Scheme 1) and **not** from the SN_2 reaction (step 2): if it were not the case, benzyl and allylic alcohols should react faster than butan-1-ol.

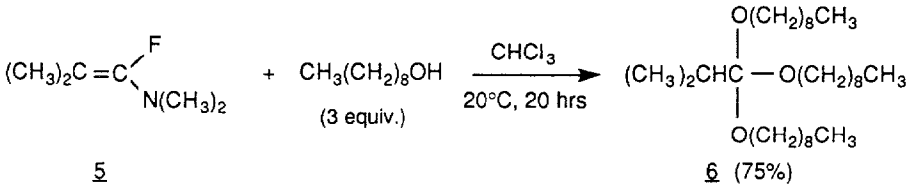
Table 3 : Relative reactivities of alcohols toward $(H_3C)_2C{=}C(Cl)N[CH(CH_3)_2]_2$ (4)

Alcohols	Product (yield %)
$CH_3(CH_2)_3OH + CH_3(CH_2)_5CHOHCH_3$	$CH_3(CH_2)_3Cl$ (100)
$CH_3(CH_2)_8OH + (CH_3)_2C(OH)CH_2CH_3$	$CH_3(CH_2)_7CH_2Cl$ (100)
$CH_3CHOHCH_2CH_2OH$	$CH_3CHOHCH_2CH_2Cl$ (94) + $[CH_3CHClCH_2CH_2Cl + CH_3CHClCH_2CH_2OH]$ (6)
$CH_3(CH_2)_3OH + (CH_3)_2C{=}CHCH_2OH$	$CH_3(CH_2)_3Cl$ (49) + $(CH_3)_2C{=}CHCH_2Cl$ (51)
$CH_3(CH_2)_3OH + PhCH_2OH$	$CH_3(CH_2)_3Cl$ (51) + $PhCH_2Cl$ (49)

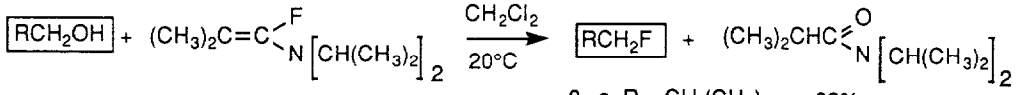
Fluorination

The reaction of 1 equivalent of tetramethyl-α–fluoroenamine 5 with nonan-1-ol in $CHCl_3$ at 20°C was slower than the corresponding chlorination. After 20 hrs a mixture of ortho ester 6 and 5 was obtained but there was no trace of fluoride. The ortho ester 6 was obtained in 75% yield when tetramethyl-α-fluoroenamine 5 was reacted with 3 equivalents of nonan-1-ol (Scheme 2). However, when reacted with N,N-diisopropyl-1-fluoro-2-methylpropenamine 7 the same alcohol yielded 1-fluorononane 8 (Scheme 2).

Scheme 2



5 6 (75%)

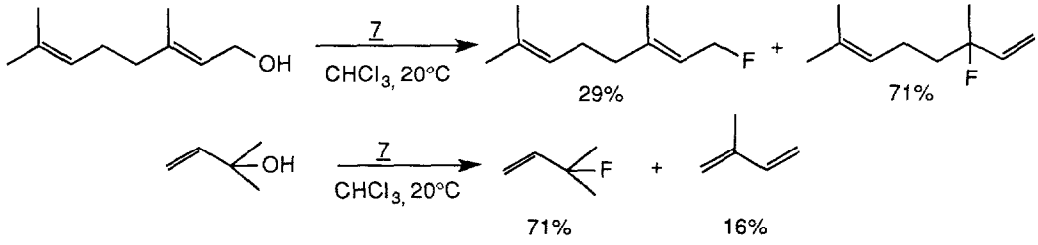


7

8 a R = $CH_3(CH_2)_7$ 93%
b R = $PhCH_2$ 85%
c R = Ph 86%

Other primary alcohols behaved similarly and gave the corresponding fluorides 8b and 8c. Preliminary studies of the reaction of 7 with allylic alcohols showed the predominant formation of the most substituted fluoride (Scheme 3).

Scheme 3



We are currently investigating the scope and limitations of this mild method of synthesis of halides, in particular fluorides and iodides. An interesting application of this method to the preparation of glycosyl halides is described in the following communication.[6]

Acknowledgement

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3) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Utz, R.; Bentler, T.; Bartkowiak, F. *Synthesis*, 1986, 361; Ernst, B.; Veenstra, S. *unpublished results.*

4) Ghosez, L.; Marchand-Brynaert, J. *Adv. Org. Chem.* 1976, 9, part 1, 421.

5) *Typical procedure :*

To a stirred solution of 0.56 ml (0.46 g, 3.5 mmol) of (+)(S) 2-octanol ($[\alpha]_D^{20}$ = +9° (neat) optical purity ~100%) in 5 ml of dry methylene chloride at 0°C is added through a syringe 0.5 ml (0.473 g, 3.5 mmol) of tetramethyl-α-chloroenamine. The reaction mixture is stirred at room temperature for 3 hours. Flash chromatography (cyclohexane/ CH_2Cl_2 9/1) yielded 0.498 g (~95%) of (-)(R) chlorooctane, $[\alpha]_D^{20}$= -31.5° ($CHCl_3$ c=4.5).

6) Ernst, B.; Winkler, T. *Tetrahedron Lett.*, 1989.

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