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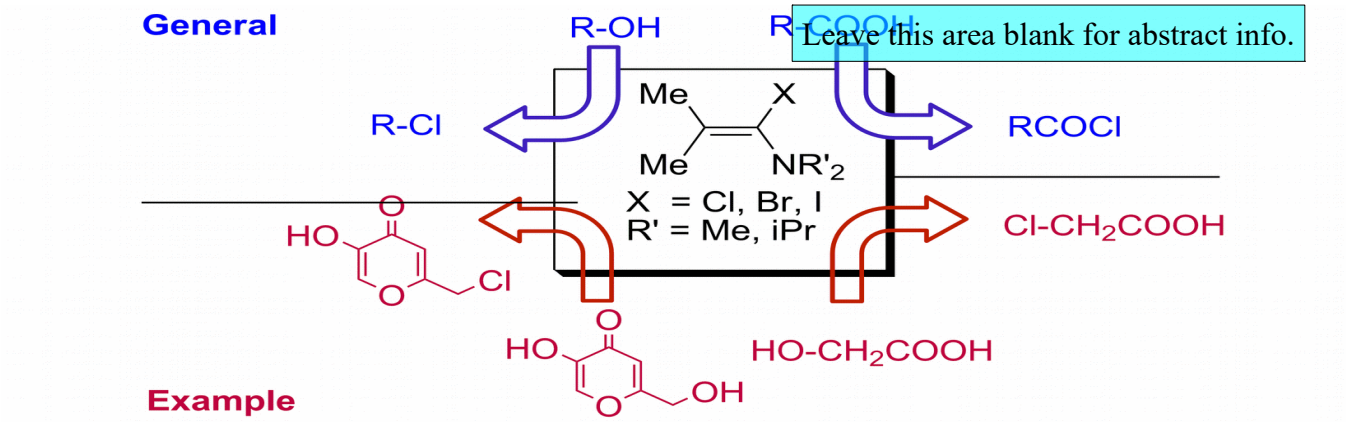

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A mild method for the replacement of a hydroxyl group by halogen. 1. Scope and chemoselectivity.

François Munyemana,[a] Isabelle George,[a] Alain Devos,[a] Alain Colens,[a] Anne-Marie Frisque-Hesbain,[a] Eduard Badarau,[b] Aurore Loudet,[b] Edmond Differding,[a] Jean-Marie Damien,[a] Jeanine Rémion,[a] Jacqueline Van Uytbergen[a] and Léon Ghosez[a,b*]

[a]*Université Catholique de Louvain, Place L. Pasteur, 1, B-1348 Louvain-la-Neuve, Belgium*
[b]*Institut Européen de Chimie et Biologie, UMR 5248-CNRS, 2, rue Robert Escarpit, F-33607 Pessac Cedex, France*

A tribute to Alan Katritsky, a great colleague and an enthusiastic scientist

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ABSTRACT

α-Chloro-, bromo- and iodoenamines which are readily prepared from the corresponding isobutyramides have been found to be excellent reagents for the transformation of a wide variety of alcohols or carboxylic acids into the corresponding halides. Yields are high and conditions are very mild thus allowing for the presence of sensitive functional groups. The reagents can be easily tuned allowing therefore the selective monohalogenation of polyhydroxylated molecules. The scope and chemoselectivity of the reactions have been studied and reaction mechanisms have been proposed.

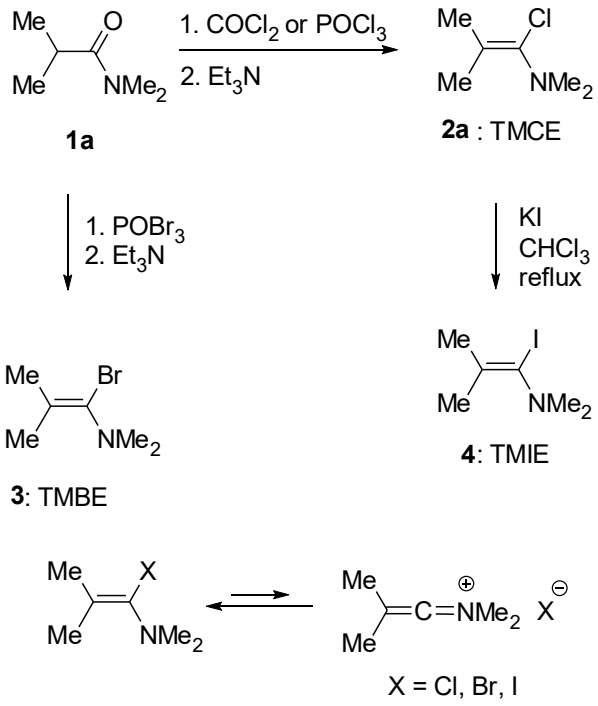
1. Introduction

Chemicals carrying hydroxyl groups are plentiful and often inexpensive. As a result chemists have developed methods for the replacement of hydroxyl groups by other functional groups containing nitrogen, sulfur, halogen atoms. The replacement of an OH group by chlorine, bromine and iodine has been much studied.[1] The most common reagents are hydrogen halides or halides derived from inorganic acids. These reagents are generally cheap and commercially available. However the strongly acidic conditions of these reactions often lead to rearrangement or decomposition products and are often uncompatible with many functional groups. Methods using milder and neutral conditions have therefore been developed.[1] The most successful methods use oxalyl chloride and a base or a combination of a phosphine or phosphite with a halogen or a carbon tetrahalide. In the latter case, however, work-up often generates a large amount of waste.

Many years ago our attention had been drawn to a publication of Speziale and Freeman reporting the conversion of alcohols and carboxylic acids into the corresponding chlorides in the presence of trichlorovinylamines.[2] In most cases reactions had to be performed at 60°–85°C and yields were moderate. These reactions *required* the presence of catalytic amounts of HCl: this indicated that the active chlorinating agent was an α-chloroiminium chloride. Thus the reaction was another variation of the chlorination of alcohols by α-chloroiminium chloride (e.g. Vilsmeier reagent).[1] A few years later, we discovered that 1-chloro-*N,N*,2-trimethylpropenylamine (tetramethyl-α-chloren-amine, TMCE) **2a** was an excellent chlorinating agent without catalytic HCl. It was easily prepared from *N,N*,2-trimethylpropanamide **1** by treatment with phosgene[3] or phosphorous oxychloride[4] followed by dehydrohalogenation with triethylamine (Scheme 1). The corresponding tetramethyl-α-bromoenamine (TMBE) **3** was similarly prepared using phosphorous oxybromide as halogenating reagent.[4] Reaction of TMCE with an excess KI in refluxing chloroform provided a convenient access to the corresponding iodoenamine (TMIE) **4**.[5]

Tetramethyl-α-chloro- and bromoenamines **2a** and **3** are thermally stable but moisture-sensitive compounds. TMIE **4** is less stable and should be used when freshly prepared. In contrast with trichlorovinylamines, all three tetramethyl-α-haloenamines **2a**, **3** and **4** are in fast equilibrium with the corresponding keteniminium halides (TMK). These are highly electrophilic species which underwent a wide variety of interesting reactions.[6]

In the early stages of our studies on α-chloroenamines, we found that they were excellent reagents for the conversion of carboxylic acids[7] and alcohols[8] into the corresponding halides. These observations did attract the attention of chemists around the world who successfully used TMCX for the replacement of OH groups by halogen. As a result, TMCE became commercially available and the reagent was described in the « Encyclopedia of Reagents for Organic Synthesis ».[6d] In contrast, these seemingly unsophisticated reactions did not meet much interest in our group and it took a while to find coworkers to examine the scope and limitations of these halogenation reactions and expand their use in synthesis. Herein we report the details of a study of the scope and chemoselectivity of this halo- dehydroxylation method.

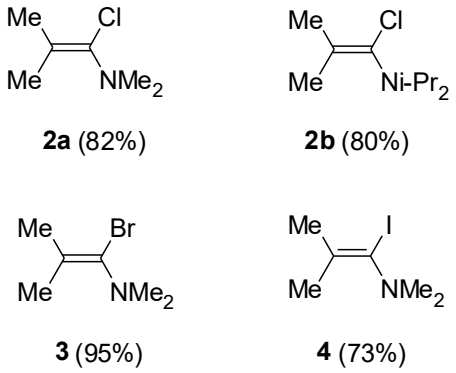


Scheme 1. Synthesis and reactivity of α-haloenamines

2. Results and discussion

2.1. Synthesis of the reagents

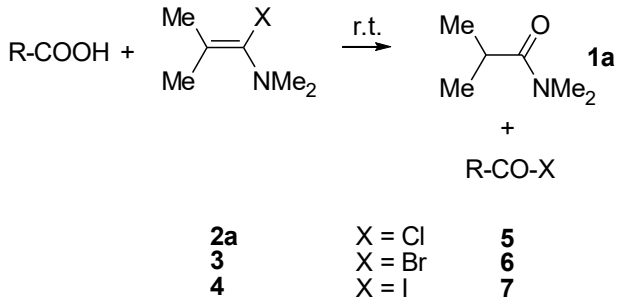
All α-haloenamines **2a**, **2b**, **3** and **4** (Scheme 2) have been prepared in good yields by the procedures outlined in Scheme 1.[4] These reactions are readily applicable to the preparation of kilogram quantities of these reagents.



Scheme 2. Yields of α-haloenamines from the corresponding amides

2.2. Reactions with carboxylic acids

α-Haloenamines reacted with carboxylic acids at room temperature or below to give the corresponding acyl halides **5**, **6**, **7** and *N,N*,2-trimethylpropanamide **1a** (Scheme 3, Table 1). The reaction consisted in adding a carboxylic acid to an equimolecular amount of tetramethylhaloenamines **2a**, **3** or **4** in solvents like dichloromethane, chloroform or acetonitrile. Yields measured by ^{1}NMR using an internal standard were essentially quantitative.



Scheme 3. Synthesis of acid chlorides, bromides and iodides

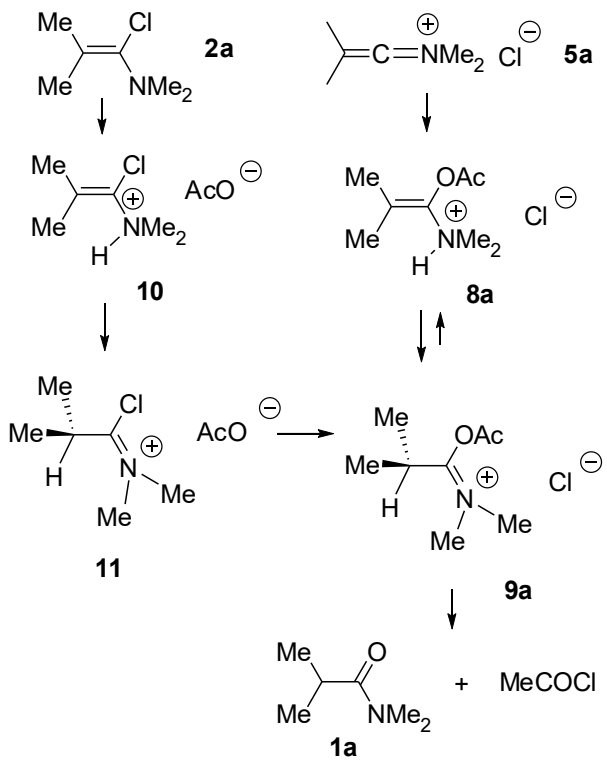
The mild and neutral conditions allowed the presence of acid-sensitive functional groups in the carboxylic acid. Another substantial advantage of the method was that it generates acid halides of high purity and *N,N'*-dimethylisobutyrylamide **1a**, a relatively inert by-product which can be recycled. Control experiments showed that a mixture of **1a** and acetyl or trifluoroacetyl chloride remained unchanged at room temperature for several days. Thus, it is not necessary to purify the acid halide which can be used *in situ.*This is particularly interesting when the acid halide is not thermally stable or when it contains sensitive functional groups. Thus the method allows the preparation of rather unstable acid halides such as **5f-k.**

We have followed by ^{1}H-NMR the reaction of TMCE **2a** (10 mM in CD_2Cl_2) with an equimolecular amount of acetic acid from – 60°C to room temperature. The temperature was increased in 5 steps to 0°C (3 min. between each step). After 1 h the mixture was brought to room temperature. Scheme 4 shows a mechanistic proposal based on this study. We favour a first step involving the reaction of the tetramethyl keteniminium chloride with acetic acid to form the protonated α-acetoxy enamine **8a**. It was indeed found that the chlorination reaction was faster in solvents known to accelerate the formation of keteniminium chloride as shown by the magnetic equivalence of the two methyl groups on the double bond in these solvents.[6] From -50°C to -35°C the amount of TMCE **2a** gradually decreased and the new acyloxy ammonium chloride **8a** was formed together with some acetyl chloride and amide **1a**. The structure of **8a** was assigned by comparison of the ^{1}H-NMR spectrum with the spectrum of the corresponding tetrafluoroborate salt **8b** prepared independently (Scheme 5). Compound **8b** was stable at room temperature but yielded acetyl chloride and amide **1a** when exposed to a source of chloride ion. Above -30°C compound **8a** gradually disappeared yielding also acetyl chloride and amide **1a**. We believe that **8a** first tautomerized to **9a** (identified by comparison with the corresponding tetrafluoroborate **9b** resulting from the tautomerization of **8b,** see Scheme 5). Compounds **9a** (Scheme 4) or **9b** (Scheme 5) would then undergo a nucleophilic substitution by attack of a chloride ion on the activated acetyl group.

Table 1 Reaction of carboxylic acids with tetramethyl-α-haloenamines

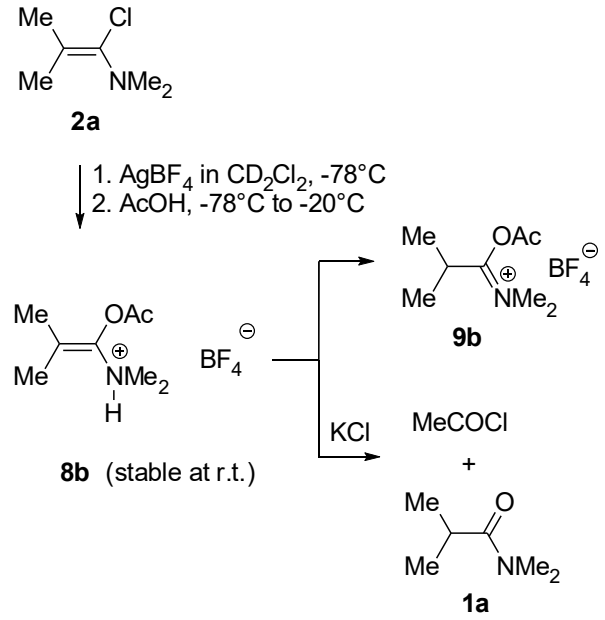
Cdp	Acid halide	t°C[a]	Time	Yield[a] %
5a	t-BuCOCl	rt	< 30min	100
5b	CH_2=CHCOCl	rt	< 30min	96
5c	Cl_3CCOCl	rt	< 30min	100
5d	N_3CH_2COCl	rt	< 30min	100
5e	$MeOCH_2COCl$	rt	< 30min	100
5f	MeCOCOCl	-20	4 h	100
5g	PhCOCOCl	-20	4h	100
5h	$(MeO)_2CHCOCl$	-40	4h	100
5i	$(EtS)_2CHCOCl$	rt	< 30min	100
5j		rt	< 30min	100
5k		rt	< 30min	100
5l		rt	< 30min	100
6a	t-BuCOBr	rt	< 30min	100
6b	CH_2=CHCOBr	rt	< 30min	100
7a	MeCOI	rt	< 30min	100
7b	PhCOI	rt	< 30min	100
7c	t-BuCOI	rt	< 30min	100

[a] reactions were performed in deuterated chloroform [b] measured by ^{1}H- NMR using an added standard (benzene or toluene) ; [c] acid chloride **5f** was quantitatively converted into methyl ester ; [d] acid chloride **5g** was converted into anilide (80%) ; [e]acid chloride **5h** was converted into *p*-methoxy-benzylamide (38%).

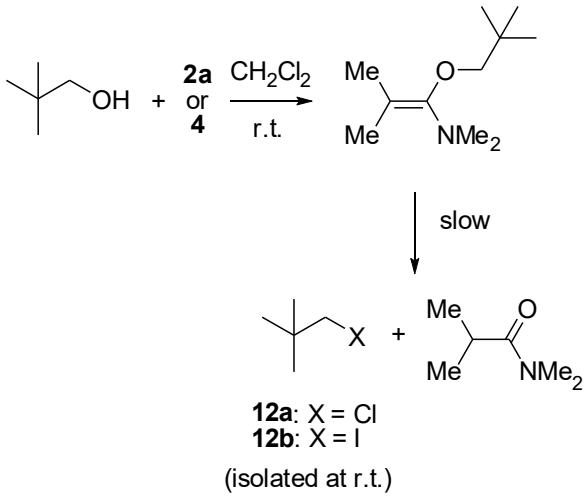


Scheme 4. Mechanistic proposal for the halogenation of carboxylix acids

Another ene-ammonium salt **10** was also observed which tautomerized to the chloroiminium salt **11**. At -20°C both ene-ammonium salts **8a** and **10** disappeared. At 0°C intermediate **11** also disappeared. We thus favour the sequence **2a - 5a – 8a – 9a** for the formation of the acid chloride. This proposal was further supported by the competition experiments described below. However with stronger acids a competitive pathway involving intermediates **10, 11** and **9a** cannot be excluded.



Scheme 5. Control experiments



Scheme 6. Reaction of neopentyl alcohol with TMCE and TMIE

2.3. Reactions with alcohols

We have also found that a wide variety of alcohols could be converted in high yields and under very mild conditions into the corresponding chlorides, bromides or iodides with this new class of halogenating agents. Typically 1 equivalent of alcohol in dichloromethane, chloroform or acetonitrile was reacted with 1-1,1 equivalent of tetramethyl α-chloro-, bromo- or iodoenamine at room temperature. The reaction was almost instantaneous and exothermic, in particular with primary and acyclic secondary alcohols. It is therefore recommended to maintain the reaction vessel at 0°C when working with multigram amounts of reactants. The order of addition of the reactants did not seem to be important. Table 2 shows that linear alcohols (entries 1-4, 12-14) gave a high yield of the corresponding halides. Neopentyl alcohol did not yield the corresponding halides under the same conditions but reacted to give an alkoxy-iminium halide which was stable at room temperature (entries 5 and 7) (Scheme 6). However, neopentyl iodide was formed in high yield after prolonged heating in dichloromethane (entries 8). The substitution reaction was slower with the corresponding chloride which required refluxing in acetonitrile for 12 h (entry 6). Cyclopropyl carbinol is known to be prone to rearrange upon treatment with a wide variety of halogenating agents.[1a] We were delighted to observe that it could be smoothly converted into the corresponding chloride, bromide or iodide when reacted with TMCE, TMBE and TMIE: yields were high and there was no trace of rearrangement products (entries 9, 10, 11).

Acyclic secondary alcohols also reacted smoothly with tetramethyl-haloenamines **2a**, **3** and **4** to give high yields of the corresponding halides (Table 3).

Table 2 Reactions of tetramethyl α-haloenamines with primary alcohols

	ROH	X	solvent	t°C	Pdt[a] (%)
1	*n*-pentanol	Cl	CH_2Cl_2	rt	97
2	*n*-pentanol	Br	$CHCl_3$	rt	96
3	*n*-pentanol	I	$CHCl_3$	rt	98
4	*n*-nonanol	Cl	CH_2Cl_2	rt	98
5	neopentanol	Cl	CH_2Cl_2	rt	0
6	neopentanol	Cl	CH_3CN	Δ,12h	72[b]
7	neopentanol	I	CH_2Cl_2	rt	0
8	neopentanol	I	CH_2Cl_2	Δ, 24h	91
9		Cl	CH_2Cl_2	rt	93[b]
10		Br	CH_2Cl_2	rt	95
11		I	CH_2Cl_2	rt	99
12	*trans* $CH_3CH=CHCH_2OH$	Cl	CH_2Cl_2	rt	99
13	*trans* $CH_3CH=CHCH_2OH$	Br	CH_2Cl_2	rt	98

14	*trans* $CH_3CH=CHCH_2OH$	I	CH_2Cl_2	rt	99

[a]measured by ^{1}H NMR using an internal standard ; [b]isolated product

Table 3. Reactions of secondary alcohols with tetramethyl α-haloenamines at r.t. in DCM

	ROH	X	Pdt[a] (%)	other products
1	dl-$CH_3CHOH(CH_2)_5CH_3$	Cl	95	
2	dl-$CH_3CHOH(CH_2)_5CH_3$	Br	96	
3	dl-$CH_3CHOH(CH_2)_5CH_3$	I	98	
4	PhCHOHPh	Cl	93[b]	
5	cyclopentanol	Cl	80	
6	cyclopentanol	Br	90	
7	cyclopentanol	I	90	
8	cyclohexanol	Cl	18	cyclohexene (82%)
9	cyclooctanol	Cl	87	cyclooctene (33%)
10	cyclooctanol	I	72	cyclooctene (28%)

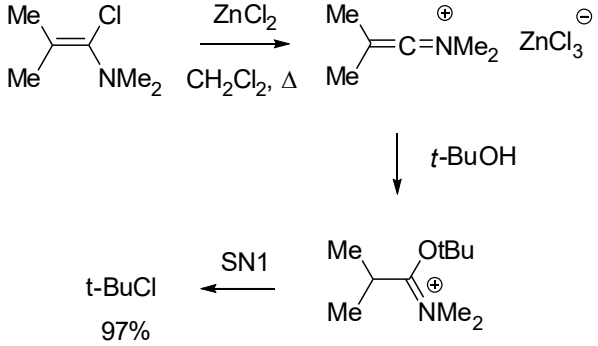
The halogenation of cycloalkanols was accompanied with the formation of the corresponding cycloalkenes : cyclopentanol exclusively yielded the substitution product (entries 5, 6, 7 but cyclohexanol mainly yielded an elimination product (entry 8). The formation of the halide was predominant in the case of cycloctanol (entries 9 and 10).

t-Butanol also reacted with tetramethyl haloenamines **2a**, **3** and **4** (Table 4)**.** The reaction was somewhat slower than with secondary and primary alcohols but still yielded substantial amounts of the corresponding halides. Yields of halide followed the order of nucleophilicity of the halide anion (entries 1, 3, 4). Comparison of entries 1 and 2 suggested that *t*-butyl chloride slowly gave isobutene in the presence of *N,N*'-dimethyl-isobutyrylamine **1**. The formation of isobutene can be suppressed by adding 1 equivalent of $ZnCl_2$ to **2a** to generate the keteniminium trichlorozincate, followed by the addition of *t*-butanol (Scheme 7). In these conditions, *t*-butyl chloride was formed in 97% yield. These findings have been successfully extended by H. Vanderhaeghe *et al.* to the chloration of 3α(β)-3β(α)-methyl-5α-cholestane using $ZnCl_2$, $SnCl_4$ or $TiCl_4$ as Lewis acid.[10]

Table 4 Reaction of *t*-butanol with tetramethyl haloenamines at room temperature in $CDCl_3$

	X	time	halide(%)[a]	other products
1	Cl	1h30	49	Isobutene
2	Cl	48h	21	isobutene
3	Br	1h30	63	isobutene
4	I	1h30	70	isobutene

[a]measured by ^{1}H NMR using an internal standard



Scheme 7. Reaction of *t*-butanol with TMCE in the presence of $ZnCl_2$

2.4. Chemoselectivity

Hydroxyl-containing functional groups are ubiquitous in organic compounds such as pharmaceuticals, agrochemicals and organic materials. Moreover they are major players in synthesis since they can be transformed into other functional groups and they undergo a variety of reactions allowing the construction of complex structures. An often encountered problem is the selective modification of an hydroxyl group in the presence of other hydroxyl-containing functional groups. This often requires the use of protecting groups, a strategy which lengthens a synthetic sequence. The problem of the selective replacement of an hydroxyl group by an halogen atom in the presence of other hydroxyl-containing functional groups has been adressed by several groups : thus primary alcohol can be selectively brominated by a mixture of Ph_3P and CBr_4 in the presence of a secondary or a tertiary alcohol.[1b] Corey's reagent -N-chlorosuccinimide/dimethylsulfide- selectively reacts with allylic and benzylic alcohols[11,1a] while AlI_3 selectively transforms allylic, benzylic and tertiary alcohols.[12,1a]

We anticipated that α-haloenamines could be readily tunable by variation of the nature of the substitution at nitrogen or (and) at C-2.

2.4.1. Alcohols

Equimolecular mixtures of alcohols (Table 5) in dichloromethane were treated by 1 equivalent of α-chloroenamines **2a** or **2b** (Scheme 2) at room temperature for 2 h. The mixture was analyzed by GLC and ^{1}H-NMR. It is clear from Table 5 that the introduction of bulky alkyl groups on the nitrogen atom significantly increased the discriminating power of the reagent between alcohols of different steric environment. Both reagents **2a** and **2b** selectively reacted with a primary alcohol (Table 5, entries 3-6) in the presence of a tertiary alcohol but the bulkier reagent **2b** was much more selective and could also discriminate between primary and secondary hydroxyl groups (entries 1 vs 2 and 9). None of the reagents could discriminate between primary alcohols of various types (entries 7, 8).

Table 5 Relative reactivities of alcohols toward **2a** and **2b**

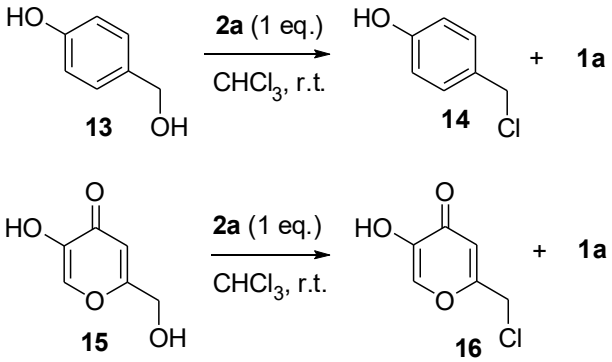
	reagent	alcohols	products	Ratio[a]
1	**2a**	$CH_3(CH_2)_3OH$ $CH_3CH_2CHOHCH_3$	$CH_3(CH_2)_3Cl$ $CH_3CH_2CHClCH_3$	6.5

2	**2b**	$CH_3(CH_2)_3OH$ $CH_3CH_2CHOHCH_3$	$CH_3(CH_2)_3Cl$ $CH_3CH_2CHClCH_3$	≥100
3	**2a**	$CH_3(CH_2)_3OH$ $(CH_3)_3COH$	$CH_3(CH_2)_3Cl$ $(CH_3)_3CCl$	8.3
4	**2b**	$CH_3(CH_2)_3OH$ $(CH_3)_2COH\ CH_2CH_3$	$CH_3(CH_2)_3Cl$ $(CH_3)_2CClCH_2CH_3$	≥100
5	**2a**	$CH_3CH_2CHOHCH_3$ $CH_3)_3COH$	$CH_3CH_2CHClCH_3$ 1,3-dithiolan-2-yl $(100\%CH_3)_3CCl$	30.9
6	**2b**	$CH_3CH_2CHOHCH_3$ $CH_3)_2COHCH_2CH_3$	$CH_3CH_2CHClCH_3$ $CH_3)_2CClCH_2CH_3$	≥100
7	**2a** or **2b**	$CH_3(CH_2)_3OH$ *trans*-$CH_3CH{=}CHCH_2OH$	$CH_3(CH_2)_3Cl$ *trans*-$CH_3CH{=}CHCH_2Cl$	≈1
8	**2a** or **2b**	$CH_3(CH_2)_3OH$ $C_6H_5CH_2OH$	$CH_3(CH_2)_3Cl$ $C_6H_5CH_2Cl$	≈1
9	**2b**	$CH_3CHOHCH_2CH_2OH$	$CH_3CHOHCH_2CH_2Cl$	16.8
10	**2b** 2 eq	$CH_3CHOHCH_2CH_2OH$	$CH_3CHClCH_2CH_2Cl$	≥24

[a]measured by GLC or (and) ^{1}H-NMR

2.4.2. Alcohols and phenols

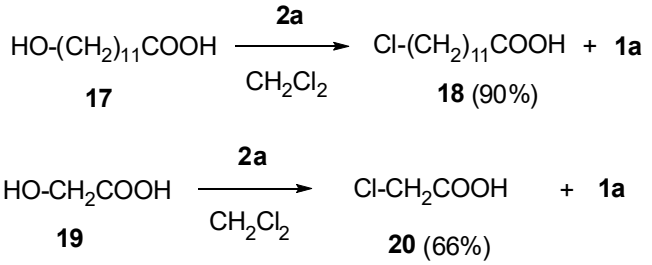
Tetramethyl-α-chloroenamine **2a** selectively reacted with the less acidic but more nucleophilic benzylic hydroxyl group of *p*-hydroxy-benzyl alcohol **13** or kojic acid **15** to give the corresponding benzylic chlorides **14** and **16** (Scheme 8). This was another observation which supported nucleophilic addition of the hydroxyl group to a keteniminium chloride as the initial step of the reaction (see Scheme 4).



Scheme 8. Reaction of TMCE **2a** with *p*-hydroxy-benzyl alcohol and kojic acid

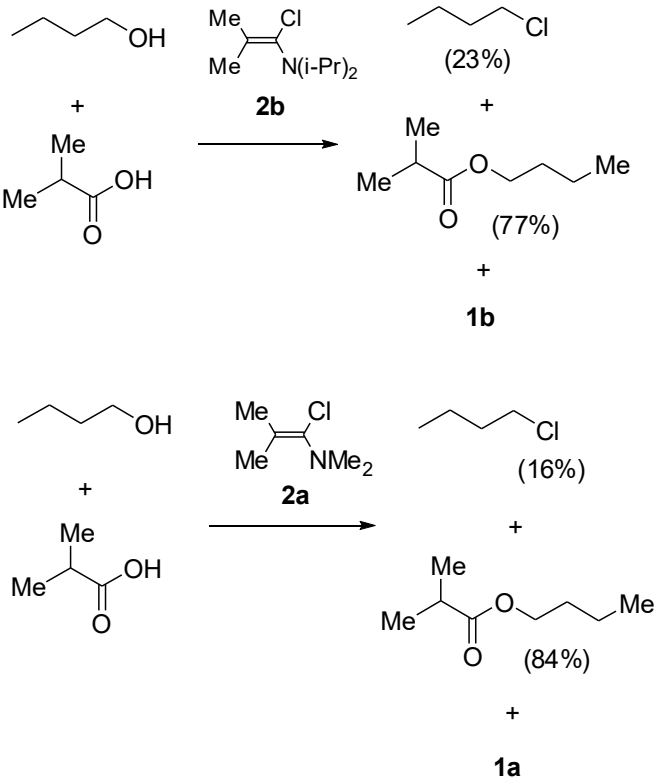
2.4.3. Alcohols and Carboxylic acids

We have also examined the relative reactivity of alcohols *vs* carboxylic acids (Scheme 9). 12-hydroxy dodecanoic acid **17** reacted with **2a** to yield almost exclusively product **18** resulting from the chloration of the primary alcohol. The remaining 10% of the material was a mixture of acid chloride $HO(CH_2)_{11}COCl$ and an ester $HO(CH_2)_{11}COO(CH_2)_{11}COOH$. Glycolic acid **19** reacted less selectively: only 66% of chloroacetic acid **20** was observed. The remaining products were unreacted glycolic acid and two esters $X\text{-}CH_2COOCH_2COOH$ (X = HO, Cl). The lower selectivity of **19** *vs* **17** can be explained by the lower nucleophilicity of the hydroxyl group due to the presence of the electron-withdrawing carboxyl group.



Scheme 9. Reaction of TMCE **2a** with hydroxyacids

An intermolecular competition between a primary alcohol and a carboxylic acid gave similar results (Scheme 10). Also no significant differences were observed between **2a** and **2b**.

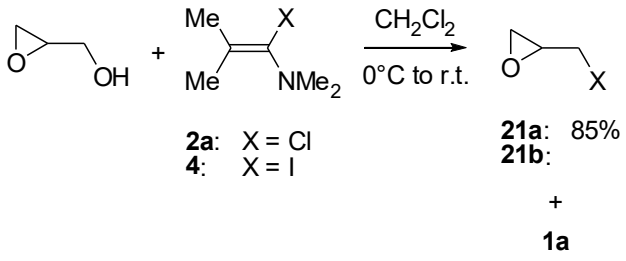


Scheme 10. Reaction of **2a** and **2b** with alcohol/acid mixtures

2.4.4. Alcohols and epoxides

Epoxides are sensitive to both acidic and nucleophilic reagents and are therefore cleavable by many halogenating reagents. It was therefore rewarding to observe that tetramethyl-α-haloenamines were efficient reagents for the chemoselective conversion of alcohols into halides in the presence of an epoxide.

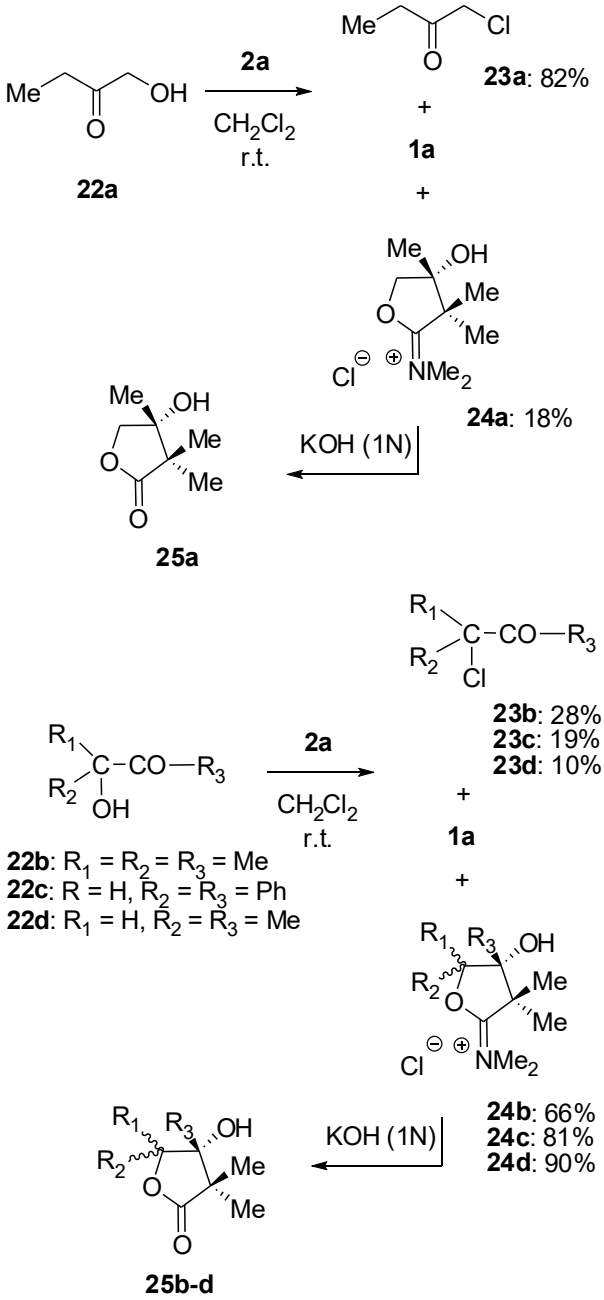
This has been illustrated by the high yield conversion of glycidol into the corresponding chloride **21a** and iodide **21b** (Scheme 11).



Scheme 11. Reaction of glycidol with TMCE **2a** et TMIE **2c**

2.4.5. α- and β-Hydroxyketones and esters

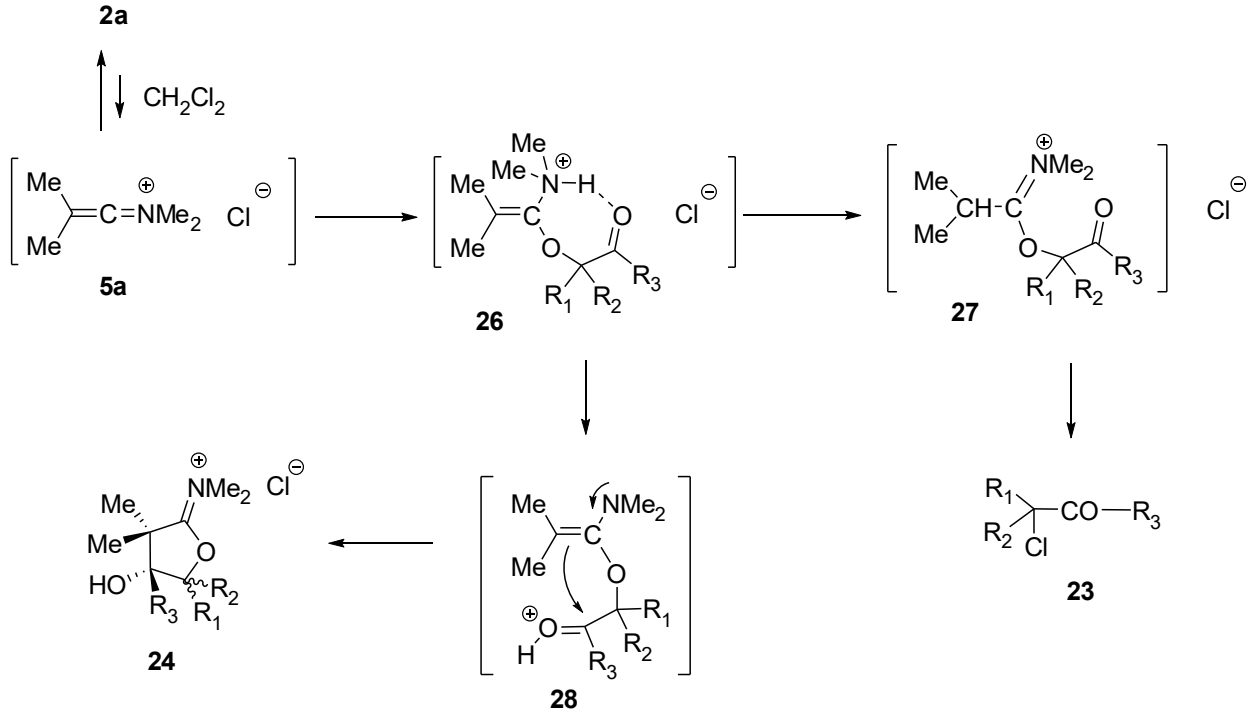
The reaction of **2a** with 1-hydroxy-2-butanone **22a** yielded the desired chloride **23a** (Scheme 12). A minor product was identified which was assigned structure **24a**. Iminium salts **24b-d** became the major products of the reaction of **2a** with ketones **22b-d** bearing a secondary or tertiary alcool function at the α-carbon atom. All iminium salts could be hydrolyzed to the corresponding γ-lactones **25a-d**. In the case of **22b** a small amount (6%) of elimination product $H_2C{=}C(CH_3)COCH_3$ was also observed. It is thus clear that α-haloenamines are not suitable for the halogenation of ketones bearing an α-secondary or tertiary alcohol function. The formation of the cyclic iminium salts **24** could be easily explained on the basis of the mechanism proposed in Scheme 13.



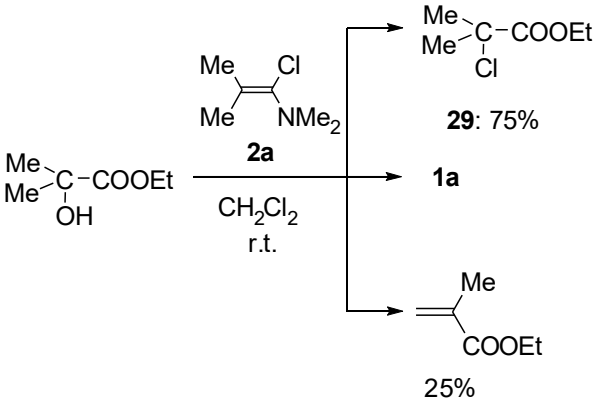
Scheme 12. Reaction of TMCE **2a** with α-hydroxyketones

The first step of the reaction would be the addition of the alcohol group to the keteniminium chloride in fast equilibrium with **2a** to generate **26.** This intermediate could then undergo a prototropic shift to generate iminium salt **27** from which chloride **23** should be easily formed. Intermediate **26** could also lead to **28** which could then cyclize to iminium salt **24**.

No cyclic iminium salt was observed upon treatment of ethyl 2-hydroxyisobutyrate with **2a**: the reaction yielded a 3 :1 mixture of the corresponding chloride **29** and ethyl methacrylate resulting from an elimination of HCl (Scheme 14). Methyl mandelate gave a lower proportion of chlorinated product **30.** The major product was again an iminium salt **31** (Scheme 15)**.**

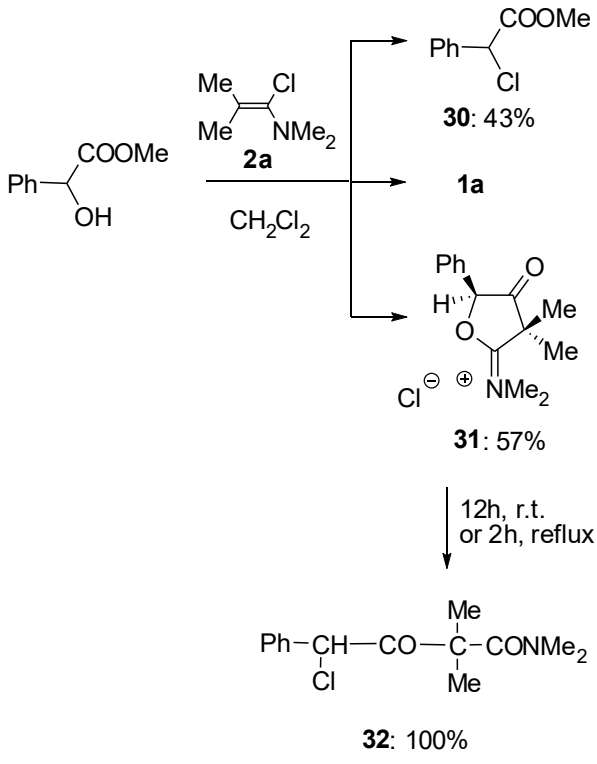


Scheme 13. Proposed mechanism for the formation of cyclic iminium salts **24**



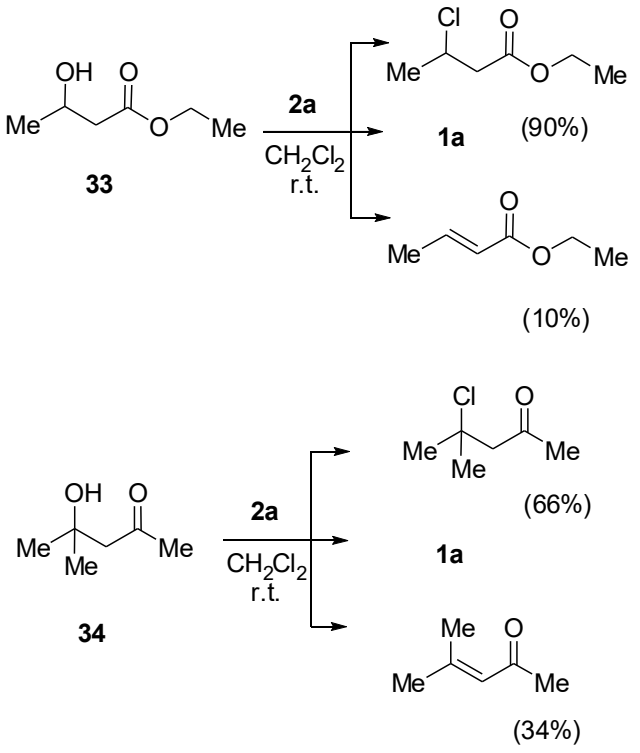
Scheme 14. Reaction of TMCE with ethyl 2-hydroxyisobutyrate **29a**

Interestingly, upon heating for 2 hours in dichloromethane, compound **31** underwent a ring opening reaction to yield **32**. Remarkably, this « Claisen-like » condensation took place under mild and neutral conditions and generated a quaternary carbon atom. We have not explored the scope of this interesting sequence (Scheme 15).



Scheme 15. Reaction of TMCE with methyl mandelate

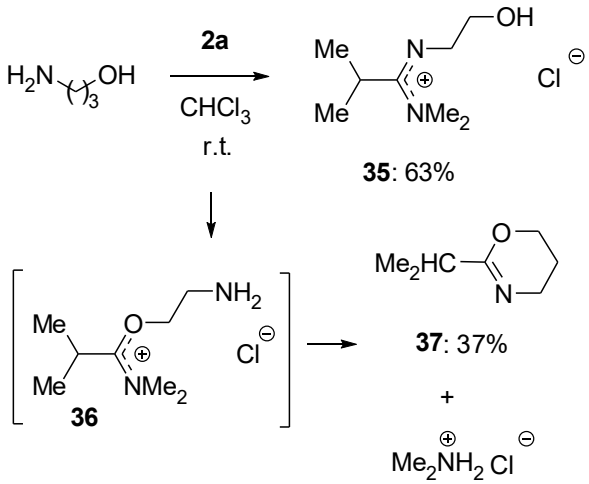
Tetramethyl-α-chloroenamine could be efficiently used for the replacement of hydroxyl by chloride in β-hydroxyesters and ketones (Scheme 16). In both cases, some elimination products were also obtained. Elimination was a minor side-reaction with ester **33**. Remarkably ketone **34** mainly yielded a substitution product in spite of the presence of a tertiary alkyl chloride and a fairly acidic α-proton. These observations further underline the power of this new method of halogenation which takes place under quasi-neutral conditions.



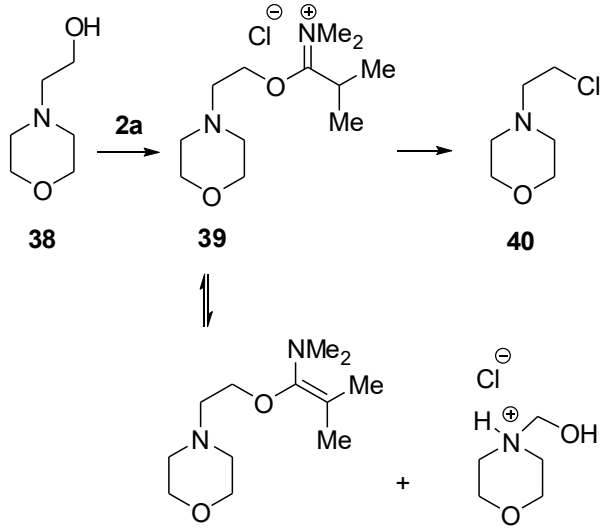
Scheme 16. Reaction of TMCE with β-hydroxyesters and ketones

2.4.6. Aminoalcohols

Primary and secondary amines are known to react fast with α-chloroenamines. As a result, the presence of an unprotected primary or secondary amine precluded the transformation of an alcohol into a halide using an α-haloenamine. The amine generally reacted faster but often mixtures of products were observed as illustrated in Scheme 17 for the reaction of 3-aminopropanol-1 with **2a.** The major product **35** resulted from the attack of the primary amine on the electrophilic carbon atom of **2a**. The minor product **37** probably resulted from the cyclization of **36** resulting from the addition of the alcohol to **2a**. The substitution of OH by halogen was successful when the amine was tertiary. The reaction of **38** with **2a** (Scheme 18) yielded almost quantitively the corresponding chloride **40.** The problem was to avoid the precipitation of the ammonium salt which could result from the deprotonation of iminium salt **39**. This did not occur in solvents like $CHCl_3$ or CH_2Cl_2.

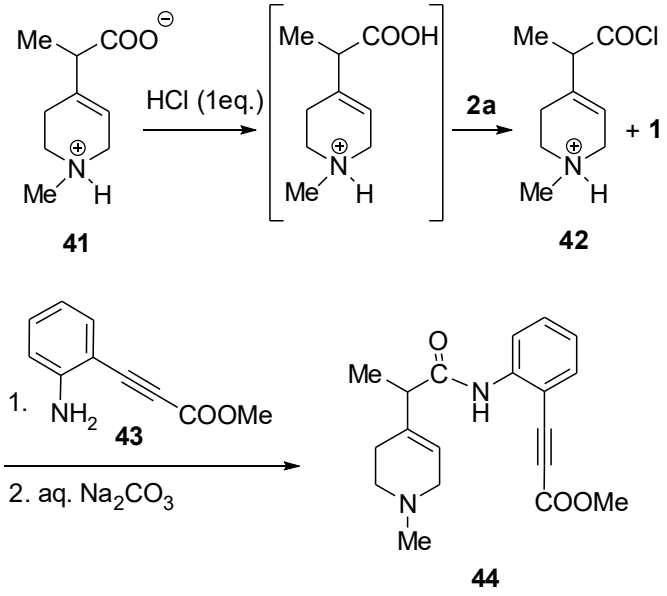


Scheme 17. Reaction of TMCE with a primary aminoalcohol



Scheme 18. Reaction of TMCE with a tertiary aminoalcohol

Another application of this mild method of halogenation is shown in Scheme 19. In another synthetic project we had to couple β,γ- unsaturated aminoacid **41** with the poorly nucleophilic substituted aniline **43**.[14] All classical peptide coupling methods led to some isomerisation of the double bond. We thus decided to effect the coupling reaction *via* acid chloride **42**. The zwitterionic aminoacid was first converted into the hydrochloride by addition of 1 equivalent of HCl then treated by **2a** in dichloromethane at room temperature for 1 h. The reaction led to the unrearranged acid chloride **42** and amide **1** contaminated by traces of the corresponding acid anhydride. Addition of aniline **43** in the presence of triethylamine yielded 70% of pure coupling product **44.**



Scheme 19. Reaction of TMCE with a sensitive β,γ-unsaturated carboxylic acid

3. Conclusions

We have examined in details the scope and chemoselectivity of the reaction of α-chloro-, bromo- and iodoenamines **2**, **3** and **4** with a variety of hydroxyl-containing molecules. The net result of the reaction is the substitution of the hydroxyl group by Cl, Br, I. The reagents are easily and inexpensively prepared from the

corresponding *N,N'*-dialkyl isobutyramide. Some are commercially available. The reaction takes place at room temperature (or lower) under neutral conditions. The other product of the reaction is the isobutyramide which can be recycled. The halide is easily separated from the amide but, in many cases, it can be used *in situ* without purification. The scope of the method is broad. An interesting feature of this method is the chemoselectivity. Many functional groups are tolerated. In addition it is possible to selectively transform polyols into monohalogenated derivatives. The reagents can indeed be tuned for this purpose. In future publications we will describe further applications of these reagents and discuss in details the stereochemistry of the substitution reaction.

4. Experimental section

4.1. General

All reactions were carried out under argon atmosphere in freshly dried solvents. Chlorinated solvents (chloroform, dichloromethane carbon tetrachloride…) were dried over P_4O_{10} then distilled. Triethylamine was dried over solid KOH, distilled and kept over KOH. Alcohols were dried over Mg/I_2 then distilled. Commercial reagents were purchased at the highest available quality and used as such. ^1H NMR spectra were recorded at 60 MHz (Varian T 60), 200 MHz (Varian Gemini-200 and XL-200, 300 MHz (Brücker Avance 300) and 500 MHz (Brücker AM 500). ^{13}C NMR spectra were recorded at 50 MHz (Varian Gemini-200, VXR-200). Infra-red spectra were recorded on a Perkin-Elmer 681 spectrometer. ^1H and ^{13}C chemical shifts are expressed in part per million (ppm) with respect to tetramethylsilane as internal standard. Mass spectra were recorded on Varian Mat 44 and Finnigan Mat-TSQ 70 using electronic impact at 70 eV, chemical ionization (100 eV, acetone or mixture of nitrogen oxide and methane) or FAB (70eV). Flash chromatography was performed using silica gel 60 (230-400 Mesh). Thin layer chromatography was performed using silicagel 60 F_{254}. GLC chromatography was performed using Varian Aerograph 1400 (detector FID, nitrogen) or Carlo Erba Fractovap (detector FID, nitrogen) on either a SE_{30} column or a capillary column type 3700 (length 30 m, polydimethylsiloxane). α-chloro,-bromo, and -iodoenamines **2a, 2b, 3** and **4** were prepared following the procedures previously described.[4a,4b,5]

4.2. General procedures for the reaction of α-haloenamines with oxyacids and alcohols

Reactions were performed under dry argon atmosphere under magnetic stirring. In **procedure A,** the alcohol was introduced through a syringe into a 0.5 – 1M solution of the α-haloenamine (usually 1.1 eq.) in freshly dried chloroform or dichloromethane or the corresponding deuterated solvents. The reactions were quite exothermic. When performed on a preparative scale, the alcohol was added at 0°C, and then the mixture was left at room temperature for 0.5 to 3 h. In **procedure B**, the α-haloenamine was introduced into a solution of alcohol in the same solvents at 0°C. It was shown that both procedures gave identical results. In few cases involving the preparation of unstable halides, the halogenation was effected at lower temperature (see **Scheme 3**) for up to 4 h.

Yields were determined after removal of the solvent either by ^1H NMR using an added standard (usually benzene or toluene) or by GLC. In some cases the halides were purified by distillation or flash chromatography. The isolated yields were always very close to those measured by NMR or GLC. *Most of the halogenation products obtained in this study were known compounds:* their spectroscopic properties have been shown to be identical to those reported in the literature and will therefore not been reported here.

4.3. Reaction of α-haloenamines with acids

4.3.1. Synthesis of 2,2-dimethoxyacetic acid chloride **5h**

Lithium hydroxide monohydrate (89.5 mmol, 3.75 g, 1.2 eq.) was added at 0°C to a solution of methyl dimethoxyacetate (74.6 mmol, 10 g, 1 eq.) in dioxane (45 ml) and water (45 ml). The mixture was stirred for 1h at 0°C and one additional hour at room temperature. Sodium hydroxide (1M aq. soln., 75 ml) was subsequently added and the mixture extracted with diethyl ether (3 x 75 ml). The recovered aqueous layer was acidified with hydrogen chloride (6N aq. soln.) until a pH of 1-2 then the organics extracted with diethyl ether (3 x 75 ml). The combined organic layers were subsequently dried with magnesium sulphate, filtrated and the solvent slowly evaporated under reduced pressure to conduct to the desired carboxylic acid in a quantitative yield. Colorless liquid; Yield: 99 %; M = 120.1 g / mol; ^1H NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 6H), 4.85 (s, 1H), 10.32 (ls, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.1 ($2CH_3$), 98.6 (CH), 170.7 (C_q).

Tetramethyl-α-chloroenamine (2.5 mmol, 0.33 ml, 1 eq.) was added dropwise, under inert atmosphere at -40°C, to a solution of the previously obtained carboxylic acid (2.5 mmol, 0.3 g, 1 eq.) in dry deuterated chloroform (2.5 ml). A complete conversion to the acid chloride **5h** (one hour at -40°C) was observed by NMR: ^1H NMR (300 MHz, $CDCl_3$) δ 3.46 (s, 6H), 4.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.6 ($2CH_3$), 103.5 (CH).

4.3.2. Synthesis of α-acetoxy-eneammonium tetrafluoroborate **9b**

100 µl (0.77 mmol, 1.1 eq.) TMCE **2a** was added to a solution of dry silver tetrafluoroborate (152 mg, 0.78 mmol, 1.1 eq.) in 2 ml deuterated dichloromethane at -78°C. After 10 min, 40 µl (0.7 mmol, 1 eq.) acetic acid were added to the mixture and the temperature was raised to 20°C. The mixture essentially contained **9b** (95%) contaminated with around 5% of the corresponding iminium tetrafluoroborate. The spectroscopic data indicated that two rotamers of **9b** were present.

Major : ^1H NMR (200 MHz) : δ 8.30 (1H, s, NH), 3.09 (6H, d, J = 5 Hz, NCH_3), 2.37 (3H,s, $COCH_3$), 1.96 and 1.63 (6H, s for CH_3) ; ^{13}C NMR (50 MHz) : δ 157.8 (**C**=O), 133.3 (=**C**-O), 121.7 (**C**-CH_3), 44.5 (N-**C**H_3), 20.2 (CO**C**H_3), 18.5 and 16.9 (C**C**H_3).

Minor : ^1H NMR (200 MHz) : δ 8.30 (1H, s, NH), 3.11 (6H, d, J = 5 Hz, NCH_3), 2.37 (3H, s, $COCH_3$), 1.99 and 1.67 (6H, s for CH_3) ; ^{13}C NMR (50 MHz) : δ 168.2 (**C**=O), 132.4 (=**C**-O), 122.5 (**C**-CH_3), 43.8 (N-**C**H_3), 20.2 (CO**C**H_3), 18.7 and 17.1 (C**C**H_3).

4.3.3. Tautomerization of **9b** to **10b**

2 µl (0.04 mmol, 0.02 eq.) were added at room temperature to the crude solution of **9b** obtained in *4.3.2.* The reaction was stopped when **9b** was completely transformed into its more stable tautomer **10b**. ^{1}H NMR (200 MHz) : δ 3.42 and 3.32 (6H, s, NCH_3), 2.16 (3H, s, $OCCH_3$), 1.34 (6H, d, J = 7 Hz, $CHC\mathbf{H}_3$); ^{13}C NMR (50 MHz) : δ 180.3 (O-C=N), 177.5 (O-C=O), 40.6 and 39.6 (N-CH_3), 30.5 (CH), 20.0 (OC-CH_3), 17.2 ($HC(CH_3)_2$).

4.4. Reaction of α-haloenamines with alcohols

4.4.1. Neopentyl chloride: the compound was not formed upon treatment of neopentyl alcohol with **2a** at room temperature but was obtained in 72% yield by refluxing an acetonitrile solution of the reactants for 24 h.

4.4.2. Neopentyl iodide: a mixture of 1g (4.4 mmol) tetramethyl iodoenamine **4** and 0.44 ml (4.1 mmol) neopentyl alcohol in 5 ml dichloromethane was refluxed for 12 h. Neopentyl iodide was purified by distillation. Yield: 0.74 g, 74%. Identical with an authentic sample.

4.4.3. Cyclopropylcarbinyl chloride, bromide and iodide: tetramethyl haloenamines **2a**, **3** or **4** (1.1 eq.) were added at 0°C to a solution of cyclopropyl carbinol in dry dichloromethane, then left at room temperature for 30 min. The cyclopropyl halides were quickly distilled under vacuum (bath temperature 60°C) to avoid the formation of cyclobutyl and homoallylic halides. The halides were identical to authentic samples.

*4.4.4. Reaction of t-butanol with **2a** in the presence of zinc dichloride :* 0.72 ml (5.1 mmol) tetramethyl-α-chloroenamine **2a** was added to a solution of 0.697 g (5.1 mmol) $ZnCl_2$ in 5 ml dichloromethane.The mixture was refluxed for 1 h then cooled down to 0°C. 471 µl (5 mmol) *t*-butanol were added and the mixture was left at room temperature for 2 h. The crude mixture only contained *t*-butyl chloride and amide **1a**. Yield: 97% (estimated on the basis of H-NMR from the crude mixture). No isobutene was detected.

4.5. Chemoselectivity

4.5.1. Competition reactions: general procedure

An equimolecular solution of the two alcohols was added to α-chloroenamine **2a** or **2b** at room temperature. In each case the corresponding isobutyramide **1a** or **1b** was obtained quantitatively. The mixtures were analyzed by GLC. Products were identical with authentic samples.

4.5.2. Chloro-dehydroxylation of kojic acid **15:** the reaction of 0.968 g (6.8 mmol) of kojic acid with 1 g (7.5 mmol) **2a** for 3 h in 5 ml CH_2Cl_2 yielded quantitatively the corresponding chloride **16 .** ^{1}H NMR (200 MHz, acetone-d_6): 8.08 (s, 1H), 6.59 (s, 1H), 4.63 (s, 2H); ^{13}C NMR (50 MHz, DMSO-d_6): 174 (CO), 162.1, 146.4, 140.5, 113.6, 41.5.

4.6. α- and β-Hydroxyketones and esters

*4.6.1. Reaction of 1-hydroxy-2-butanone **22a** with **2a***

Procedure A: 0.567 g (6.4 mmol) of **22a**, 0.945 g (7.67 mmol) **2a**, 7 ml CH_2Cl_2, 1 h at r.t.; ratio 4.6 / 1 1-chloro-2-butanone **23a** / iminium salt **24a** measured by ^{1}H NMR . 1-Chloro-2-butanone **23a** 0.445 g (65%) was purified by distillation (30°C/13mm Hg) and was found identical with an authentic sample: ^{1}H NMR (200 MHz, $CDCl_3$): 4.12 (s, 2H), 2.63 (q, J = 7.3 Hz, 2H), 1.12 (t, J = 7.3 Hz, 3H). The minor product **24a** was not purified. The structure was proposed on the basis of its ^{1}H NMR spectrum and the comparison with the spectroscopic properties of **24b-d.** ^{1}H NMR (200 MHz, $CDCl_3$): 4.97 (d, J = 9.7 Hz, 1H), 4.71 (d, J = 9.7 Hz, 1H), 3.61 (s, 3H), 3.50 (s, 3H), 1.68 (s, 3H), 1.44 (q, J = 7.3 Hz, 2H), 1.43 (s, 3H), 1.09 (t, J = 7.3 Hz, 3H).

4.6.2. Reaction of 2-methyl-2-hydroxy-3-butanone **22b** *with* **2a**

Procedure B: 0.328 g (3.2 mmol) **22b**, 0.5 ml (3.5 mmol) **2a**, 2h in 5 ml CH_2Cl_2, r.t. Products ratio measured by ^{1}H NMR : 11/4.7/1 iminium **24b**/α,β-unsaturated ketone/ chloride **23b**. Both chloride and unsaturated ketone were distilled off from the reaction mixture. They were identical with authentical samples. ^{1}H NMR **23b** (200 MHz, $CDCl_3$): 2.39 (s, 3H), 1.69 (s, 6H): ^{1}H NMR $H_2C{=}CH(CH_3)COCH_3$ (200 MHz, $CDCl_3$) : 5.97 and 5.81 (m, 1H+1H), 2.34 (s, 3H), 1.87 (t, J = 1 Hz, 3H). The residue contained amide **1a** and iminium salt **24b**. ^{1}H NMR crude **24b** (200 MHz, $CDCl_3$): 3.50 and 3.39 (s, 3H + 3H), 1.69 and 1.68 (s, 3H + 3H), 1.58 (s, 3H), 1.54 and 1.21 (s, 3H + 3H).

The crude residue was dissolved in 2 ml CH_2Cl_2 and the solution was treated at room temperature with 2 ml 1N KOH for 2 h. The organic phase was washed with water and dried over $MgSO_4$. After removal of the solvent, lactone **25d** was purified by flash chromatography (SiO_2, Cyclohexane/ethyl acetate 8/2). 1.31 g (52%), Colourless crystalline solid, Fus. 89.2°C, IR (CH_2Cl_2) : 3610 cm^{-1} (OH), 1765 cm^{-1} (CO) ; ^{1}H NMR (200 MHz, $CDCl_3$) : 1.80 (s, 1H), 1.46 and 1.44 (s, 3H + 3H), 1.31 (s, 3H), 1.24 and 1.22 (s, 3H + 3H) ; ^{13}C NMR (50 MHz, $CDCl_3$) : 181.4, 88.5, 79.7, 47.6, 26.4, 23.3, 20.2, 19.2. Mass spectrum (EI): 173 $(M+H)^+$ 100% . Elemental analysis: Calcd : C : 62,767, H : 9.364 ; Found : C : 62.80, H : 9.41.

*4.6.3. Reaction of benzoin **22c** with **2a***

Procedure B: 1.444 g (6.8 mmol) benzoin **22c**, 1 g (7.5 mmol) **2a**, 7 ml CH_2Cl_2, 3 h. A 4.26/1 mixture of iminium salt **24c** and chloride **23c** was obtained as shown by ^{1}H NMR. The chloride **23c** was identical with an authentic sample: ^{1}H NMR (200 MHz, $CDCl_3$): 7.3-8 (m, 10 H_{ar}), 6.38 (s, CHCl, 1H). Compound **24c** was recrystallized from CH_2Cl_2/diethylether. 1.16 g (71%), Fus. 160-161°C; IR (KBr): 3400 cm^{-1} (OH), 1690 cm^{-1} (C=N$^+$), 1620 cm^{-1} (C=C).

*4.6.4. Reaction of 2-hydroxyisobutyrate with **2a***

Procedure B: 0.42 g (3.2 mmol) hydroxyester, 0.47 g (3.5 mmol) **2a**, 2 h. A 3/1 mixture of chloride **29** and alkene was obtained as shown by ^{1}H NMR. The spectral properties were identical with those of authentic samples. For the cpd **29**: ^{1}H NMR (200 MHz, $CDCl_3$): 4.2 (q, J = 7 Hz, 2H, CH_2), 1.78 (s, 6H, $(CH_3)_2C$), 1.3 (t, J = 7 Hz, $\underline{CH_3}CH_2$). For alkene: ^{1}H NMR (200 MHz, $CDCl_3$): 6.10 (app q, J = 1 Hz, 1H, H-C=), 5.56 (app q, J = 1.5 Hz, 1H, H-C=), 4.2 (q, J = 7 Hz, 2H, CH_2CH_3), 1.95 (dd, J_1 = 1.5 Hz, J_2 = 1, 3H, $CH_3C{=}CH_2$), 1.78 (t, J = 7 Hz, 3H, CH_3CH_2);

*4.6.5. Reaction of methyl mandelate with **2a***

Procedure A: 1.13 g (6.8 mmol) methyl mandelate, 1 g (7.5 mmol) **2a**, 3 h. As shown by ^{1}H NMR, a 1.35/1 mixture of iminium salt **31** and and chloride **30** was obtained after 3 h of reaction at room temperature. When reaction was continued for 12 h, the iminium salt slowly gives the ring-opening product **32**. The same result was obtained if the reaction was refluxed for 2 h.

For cpd **30**: ^{1}H NMR (200 MHz, $CDCl_3$): 7.3-7.5 (m, 5H, H_{ar}), 5.37 (s, 1H, C<u>H</u>Cl), 3.76 (s, 3H, CH_3O); ^{13}C NMR (50 MHz, $CDCl_3$): 169.5 (C=O), 136.3 ($C_{q\ ar}$), 129.9 ($2CH_{ar}$), 129.4 ($2CH_{ar}$), 128.5 (CH_{ar}), 59.3 (<u>C</u>HCl), 53.7 (COO<u>C</u>H$_3$). IR (CH_2Cl_2): 1760 cm^{-1} (COO);

For cpd **31**: ^{1}H NMR (200 MHz, $CDCl_3$): 7.30-7.60 (m, 5H, H_{ar}), 6.70 (s, 1H, C<u>H</u>C=O), 3.71 (s, 3H, C<u>H</u>$_3$N=C), 3.68 (s, 3H, C<u>H</u>$_3$N=C), 2.00 (s, 3H, C<u>H</u>$_3$CC=O), 1.61 (s, 3H, C<u>H</u>$_3$CC=O).

*4.6.5 Reaction of 3-hydroxy-ethylbutyrate with **2a***

Procedure B: 0.43 g (3.2 mmol) hydroxyester, 0.47 (3.5 mmol) **2a**, 4 h. A 9/1 mixture of chloride and alkene was obtained as shown by ^{1}H NMR. For chloride: ^{1}H NMR (200 MHz, $CDCl_3$): 4.4 (sept, J = 7 Hz, 1H, C<u>H</u>Cl), 4.2 (q, J = 7 Hz, 2H, -$CO_2C\underline{H}_2CH_3$), 2.7 (d, J = 7 Hz, 2H, $CHClC\underline{H}_2CO_2$-), 1.6 (d, J = 7 Hz, 3H, C<u>H</u>$_3$CHCl), 1.3 (t, J = 7 Hz, 3H, C<u>H</u>$_3$CH$_2$OCO-). For alkene: ^{1}H NMR (200 MHz, $CDCl_3$): 6.97 (dxq, J_1 = 15.6 Hz, J_2 = 6.9 Hz, 1H, $CH_3C\underline{H}$=C), 5.84 (dxq, J_1 = 15.6 Hz, J_2 = 1.7 Hz, 1H, -COOC<u>H</u>=C), 4.18 (q, J = 7 Hz, 2H, $CH_3C\underline{H}_2COO$-), 1.88 (dxd, J_1 = 6.9 Hz, J_2 = 1.7 Hz, 3H, C<u>H</u>$_3$CH=CH), 1.28 (t, J = 7 Hz, 3H, C<u>H</u>$_3$CH$_2$COO-). ^{13}C NMR (50 MHz, $CDCl_3$): 167.1 (<u>C</u>=O), 144.9 ($CH_3\underline{C}H$=CH), 123.2 (CH_3CH=<u>C</u>H), 60.3 (COO<u>C</u>H$_2$CH$_3$), 18.1 (<u>C</u>H$_3$CH=CH), 14.4 (<u>C</u>H$_3$CH$_2$COO-).

*4.6.6 Reaction of 4-hydroxy-4-methylpentan-2-one with **2a***

Procedure B: 0.37 g (3.2 mmol) kydroxyketone, 0.47 (3.5 mmol) **2a**, 2 h. A 2/1 mixture of chloride and alkene was obtained as shown by ^{1}H NMR. For chloride: ^{1}H NMR (200 MHz, $CDCl_3$): 2.95 (s, 2H, CH_2COCH_3), 2.2 (s, 3H, $COCH_3$), 1.7 (s, 6H, $(CH_3)_2CCl$). For vinylketone: ^{1}H NMR (200 MHz, $CDCl_3$): 6.1 (m, 1H, <u>H</u>C=C), 2.2 (s, 3H, COC<u>H</u>$_3$), 2.14 (d, J = 1.2 Hz, 3H, C<u>H</u>$_3$C=), 1.89 (d, J = 1.2 Hz, 3H, C<u>H</u>$_3$C=).

4.7. Aminoalcohols

*4.7.1 Reaction of aminopropanol with **2a***

Procedure B: 0.27 g (3.54 mmol) aminoalcohol, 0.47 g (3.54 mmol) **2a**, 1 h at r.t. A 1.7/1 mixture of chloride **35** and iminoether **37** was obtained as shown by ^{1}H NMR. The products could be subsequently separated by precipitation with dry diethyl ether: the iminoether is soluble in Et_2O, while the chloride salts precipitate from the crude mixture. For chloride **35**: ^{1}H NMR (200 MHz, $CDCl_3$): 7.70 (m, 1H, N<u>H</u>), 3.80 (t, J = 5.5 Hz, 2H, -$CH_2C\underline{H}_2OH$), 3.74 (t, J = 5.5 Hz, 2H, $NHC\underline{H}_2CH_2$), 3.4 (sept, J = 7 Hz, $(CH_3)_2C\underline{H}$), 3.35 (s, 6H, $N(CH_3)_2$), 1.84 (pent, J = 5.5 Hz, J = 5.5 Hz, 2H, $C\underline{H}_2CH_2OH$), 1.43 (d, J = 7 Hz, 6H, $CH(CH_3)_2$). The iminoether had the same spectral properties with those reported in the literature.[13]

*4.7.2 Reaction of 2-morpholinoethanol with **2a***

Procedure B: 0.84 g (6.4 mmol) alcohol, 0.95 g (7 mmol) **2a**, 12 h. For cpd **40**: ^{1}H NMR (200 MHz, $CDCl_3$): 3.72 (t, J = 4.8 Hz, 4H, $C\underline{H}_2OC\underline{H}_2$), 3.59 (t, J = 7, 2H, $C\underline{H}_2Cl$), 2.72 (t, J = 7, 2H, $NC\underline{H}_2$), 2.51 (t, J = 4.8 Hz, 4H, $C\underline{H}_2NC\underline{H}_2$). ^{13}C NMR (50 MHz, $CDCl_3$): 66.3 ($\underline{C}H_2O\underline{C}H_2$), 59.7 ($N\underline{C}H_2$), 53.0 ($\underline{C}H_2N\underline{C}H_2$), 40.1 ($\underline{C}H_2Cl$).

4.7.3 Reaction of TMCE with a sensitive β,γ-unsaturated carboxylic acid

Bubbling gaseous hydrogen chloride for 3 min. into a solution of 0.1 g (0.592 mmol) aminoacid **41** in dichloromethane followed by evaporation to dryness gave a quantitative yield of aminoacid hydrochloride : ^{1}H-NMR (60 MHz, CD_3CN) δ : 1.2 (d, J = 7 Hz , H_3C-C-COO), 2.5 (m, 2H, N-CH_2-CH_2-), 2.73 (s, 3H, N-CH_3), 3.2 (m, 3H, N-CH_2 and CH-COO), 3.6 (m, 2H, N-CH_2-CH=C), 5.5 (broad s, =CH-), 8.67 (broad s, 2H COOH and HN^+). IR (CH_3CN, cm^{-1}): 3400-2000 (COOH), 2420 (HN^+), 1715 (C=O), 1635 (C=C).

The dried residue was dissolved in 7ml dichloromethane and 0.095 ml (0.71 mmol, 1.2 eq.) of TMCE **2a** were syringed into the solution under inert atmosphere. After 1h, spectroscopic control showed the presence of acid chloride **42** and amide **1a** and traces of anhydride.

A solution of 0.104 g (0.592 mmol, 1 eq.) of aniline **43** and dry triethylamine (0.0825 ml, 0.592 mmol, 1 eq.) in 2 ml of dry dichloromethane was slowly added to the acid chloride solution and the resulting mixture was left under stirring for 2 h at room temperature. Evaporation of the solvent left a residue which was extracted with carbon tetrachloride (3 x 10 ml) to remove most of *N*-dimethylisobutyramide. The residue was dissolved in 5 ml dichloromethane and the solution was extracted with 10 ml of a saturated aqueous solution of sodium carbonate. Then, the aqueous phase was further extracted with 4 x 10 ml dichloromethane. Combining the organic phases, drying on magnesium sulfate and evaporation of the solvent yielded 165 mg of a mixture containing anilide **44**, isobutyramide **1a** and starting aniline **43.** Anilide **44** was purified by preparative TLC (ethyl acetate-cyclohexane 1:1, R_f = 0.4-0.66). Yield: 70%. ^{1}HNMR (200 MHz, $CDCl_3$) δ: 1.38 (d, 3H, H_3C-CH, J = 7.0 Hz), 2.35 (s, 3H, H_3C-N), 2.4-2.7 (broad, 4H,), 3.02 (m, 2H N-CH_2), 3.24 (q, 1H, Me-CH), 3.87 (s, 3H, H_3C-O), 5.87 (broad s, 1H, HC=C), 7.06 (ddd, 1H_{ar}, J = 7.6 Hz), 7.45 and 7.52 (dd and ddd, 2H_{ar}, J = 7.6 Hz and 7.75 Hz and 1.4)), 8.20 (broad s, 1H, NH), 8.44 (dm, 1H_{ar}). ^{13}CNMR (50 MHz, $CDCl_3$) δ: 14.5 (CH_3-C), 26.7, 45.4 (N-CH_3), 49.2 (CH-Me), 51.7 (CH_2-N) ; 52.6 (CH_3-O), 54.2 (CH_2-N), 81.7 (acetylenic C), 86.9 (acetylenic C), 107.8 (C_{ar}-C), 119.3 (C_{ar}), 123.2 (C_{ar}), 123.5 (HC=), 132.0 (C_{ar}), 133.1 (C_{ar}), 135.5 (quaternary C), 140.8 (C_{ar}-NH), 153.5 (CO), 171.8 (OC-NH). IR (DCM, cm^{-1}) : 3400 and 3370 (NH), 1710 and 1695 (CO ester and amide). Mass (IE): 326($M^{+\cdot}$).

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