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ARTICLE

Chemoselective Homologative Preparation of Trisubstituted Alkenyl Halides from Carbonyls and Carbenoids

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The chemoselective synthesis of trisubstituted alkenyl halides (Cl, Br, F, I) starting from ketones and aldehydes and lithium halocarbenoids is reported. Upon forming the corresponding tetrahedral intermediate adduct, followed by the addition of thionyl chloride, a selective E2-type elimination is triggered, thus furnishing the targeted motifs. The transformation takes place under full chemocontrol: various sensitive functionalities (*e.g.* ester, nitrile, nitro, halogen groups) can be placed on the starting materials, thus documenting a wide reaction scope, as well as, the application of the technique to biologically active substances.

The interest towards the alkenyl halide moiety encompasses distinct areas of Organic Synthesis; in fact, it represents a versatile motif well suited for undergoing further elaborations through conceptually different regimes.[1] As a consequence of the unique electronic environment imparted by the halogen, the material can be advantageously employed in C-C or C-heteroatom bond formations (either *via* polar metalation or transition-metal catalyzed sequences – Scheme 1).[2] Moreover, it is expressed in some natural products (mainly in the form of vinyl-type chlorides) and can also be present in medicinally relevant structures or agrochemicals.[3]

The desired substitution pattern – and consequently the stereochemistry - of the alkenyl cluster dictate the rationale for selecting the most adequate preparative route. Accordingly, the hydrohalogenation of alkynes offers a valuable strategy tuneable in both *syn*- and *anti*- Markovnikov-type additions also when organic halides replace pure mineral acids (HX – Scheme 1, *path 1.a*).[4] Although various transition-metal catalyzed approaches have been developed, procedures leading to alkenyl fragments featuring the four halogens have been rarely described.[5] Notwithstanding, previously considered elusive internal alkynes can nowadays be used as competent starting materials.[5c,6] More traditional methods are paved on the conversion of carbonyl groups into vinyl halides, as well illustrated by the so-called Barton synthesis which unfortunately shows high substrate sensitivity and may require the intermediate preparation of capricious species (*e.g.* hydrazones - Scheme 1, *path 1.b* - *left*).[7] In this context, although the Prati's modification addresses these difficulties, it still remains challenging for common materials such as benzophenones.[8] Alternatively, vinylic-type nucleophilic substitutions conducted on functionalized alkenes in transition-metal catalyzed reactions have been also reported (Scheme 1, *path 1.b – right*).[9] From a specular perspective, the same carbonyl moiety constitutes a placeholder for a halo-alkene through a formal homologative event. Wittig-like methodologies with α-halosubstituted phosphorous ylides can furnish both *E*- or *Z*- olefins[10] but, due to the highly basic conditions required, undesired eliminations to alkynes or reductions to methylene units could affect the chemoselectivity (Scheme 1, *path 2.a*).[11] In general, gaining remarkable control during these processes is somehow counterbalanced by the restriction of the protocol to more electrophilic carbonyls (aldehydes). In this sense, the venerable Takai halo-olefination furnishes *disubstituted* alkenes starting from aldehydes and a haloform in the presence of somehow problematic Cr(II) salts (Scheme 1, *path 2.b*).[12] However, engaging ketones proved to be more challenging and usually needs the employment of bimetallic species (*e.g.* Mg-$TiCl_4$) to generate an adequately reactive nucleophile (Scheme 1, *path 2.c*).[13] Significantly, the inconvenient manipulability of fluoroform (bp -82 °C)[14] precluded the adoption of these protocols for the preparation of alkenyl fluorides.

Cognizant of the excellent reactivity of lithiated halomethanes towards carbonyls (ketones and aldehydes) generating tetrahedral nucleophilic addition intermediates,[15] we reasoned that the induction of a proper eliminative event would deliver the desired halo olefins (Scheme 1, *path 3*). To make productive the concept, it became critical individuating an adequate reactant (FG-B) able to assist the β-elimination – directly on the tetrahedral intermediate - during the C-O bond scission. Herein,

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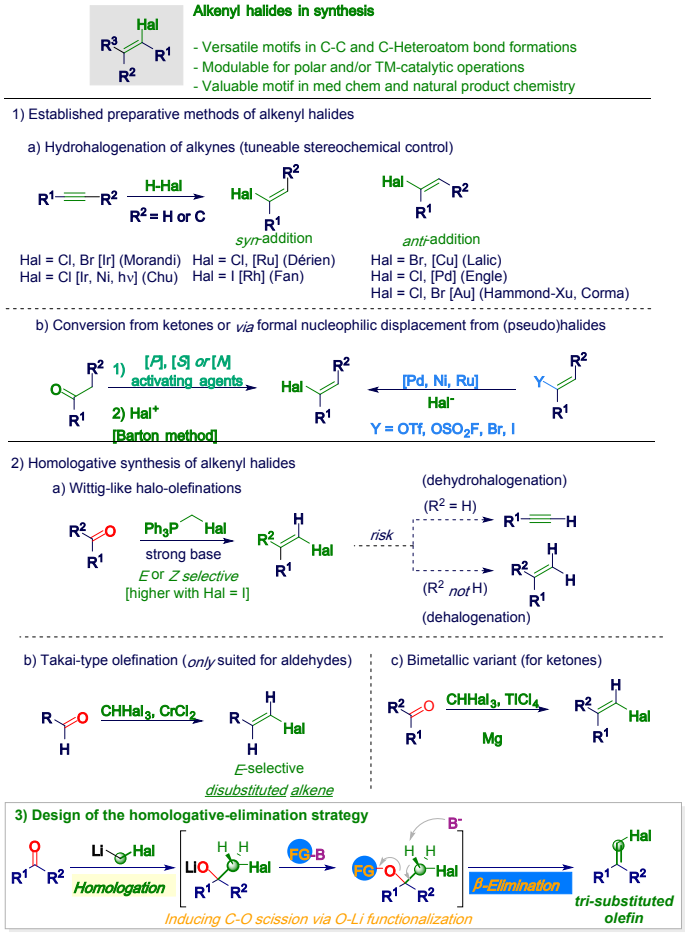
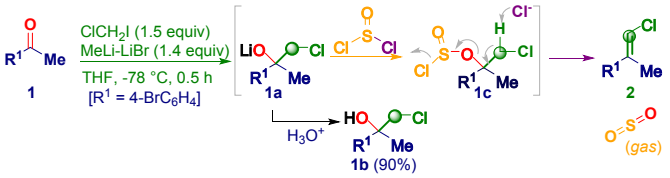
we report a robust and flexible protocol harnessed on a sequential homologation-elimination realized on a carbonyl precursor, thus furnishing alkenyl halides in high yield and stereo-preference for the more stable configurational isomer.



Scheme 1. General context of the presented work.

4-Bromoacetophenone (**1**) was selected as a suitable model compound – susceptible of base-mediated enolate formation - in the reaction with the basic carbenoid $LiCH_2Cl$ (Table 1). The constitutive presence of the exchangeable bromine atom would permit to assess the chemocontrol of the transformation in the presence of the lithiated carbanion-type species. Levering on our previous studies on homologative/deoxygenative sequences,[16] 1.4 equiv of carbenoid – generated from 1.5 equiv of $ClCH_2I$ and 1.4 equiv of MeLi-LiBr at -78 °C in THF – we could ascertain the complete conversion (upon acidic quenching) of the ketone into chlorohydrine **1b** (90% yield). With this confirmation in hand, we studied the subsequent E2-type elimination run on the lithiated chlorohydrin **1a** triggered by an external agent. Thus, by slowly adding $SOCl_2$ (1.5 equiv) at -78 °C and stirring for 10 min followed by 30 min at ambient temperature, the desired *E*-chloroalkene (**2**) was obtained in 86% yield and *E*/*Z* > 99:1 ratio, as deducted by NOESY experiments (entry 1). Some points merit mention: a) adding $SOCl_2$ to the lithiated intermediate cooled at 0 °C had a detrimental effect, since the formation of impurities was observed by ^{1}H-NMR of the reaction crude and the *E*/*Z* ratio sensitively diminished (entry 2); b) continuing the stirring at -78 °C did not induce any elimination and, the corresponding chlorosulfite intermediates could be isolated (entry 3, *vide infra*); c) the addition of bases such as DIPEA or pyridine, though enabled the formation of the alkene, was not comparable to the process carried out with only $SOCl_2$ thus, suggesting the chloride ion (released during the formation of the chlorosulfite ester) as the active base for boosting the elimination on the intermediate **1c** (entries 4-5); d) replacing $SOCl_2$ with $SOBr_2$ dwindled the chemical yield (entry 6), as well as, the use of analogous $(COCl)_2$ and phosphorous-based electrophiles ($POCl_3$, $POBr_3$, PCl_3, entries 7-10). Plausibly, the release of gaseous SO_2 at the end of the eliminative sequence accounts for the high efficiency of the transformation.

Table 1. Optimization of the reaction.



Entry	Eliminating agent (equiv)	Temperature [° C]	Reaction time (h)[a]	Yield of **2** (%)[b]	*E*/*Z* ratio of **2**
1	$SOCl_2$ (1.5)	-78 to rt	0.5	95	>99:1
2	$SOCl_2$ (1.5)	0 to rt	0.5	67	93:7
3[c]	$SOCl_2$ (1.5)	-78	2	-	-
4[d]	$SOCl_2$ (1.5)	-78 to rt	0.5	75	98:2
5[e]	$SOCl_2$ (1.5)	-78 to rt	0.5	58	98:2
6	$SOBr_2$ (1.5)	-78 to rt	0.5	82	>99:1
7	$(COCl)_2$ (1.5)	-78 to rt	0.5	63	98:2
8	$POCl_3$ (1.5)	-78 to rt	0.5	54	99:1
9	$POBr_3$ (1.5)	-78 to rt	0.5	62	99:1
10	PCl_3 (1.5)	-78 to rt	0.5	48	>99:1

[a] Reaction time refers to the stirring of the mixture after removing the cooling bath. [b] Isolated yield. [c] See Scheme 3 for the isolation of chlorosulfite intermediates. [d] DIPEA (1.3 equiv) was added after concluding the addition of $SOCl_2$; [e] Pyridine (1.3 equiv) was added after concluding the addition of $SOCl_2$.

Having demonstrated that $SOCl_2$ induces a E2-type elimination conducted on nucleophilic addition intermediates (alkoxides) – without furnishing any (OH → Cl) substitution products,[17] we then studied the scope of the method (Scheme 2). Variously aryl-substituted acetophenones were all amenable substrates, giving the corresponding trisubstituted chloro-alkenes in very high chemical yield and *E*-selectivity. Not only the whole series of halogens (**2**-**5**) – including the trifluoromethyl- analogue (**6**) - could be conveniently placed on the aromatic ring but, also substrates decorated with nitrile (**7**), ether (**10**) and ester (**13**) functionalities worked equally well, furnishing in all cases halo-olefins in >99:1 *E*/*Z ratio*. A part of simple acetophenone (**8**), the more sterically hindered *o*-methyl analogue (**9**) underwent the transformation in comparable efficiency. While using the (linear) propiophenone gave compound **11** in >99:1 *E*/*Z ratio*, switching to the highly sterically demanding *t*-butyl-phenyl ketone (**12**) reversed the ratio in favour of the *Z*-isomer. The employment of di(hetero)arylketones [benzophenones (**14**-**17**) the bis-thienyl- (**18**), the ferrocenyl- (**19**) and the bis-cyclohexyl (**20**) analogues] guaranteed the access to (mainly) (*Z*)-halo-alkenes in comparable yields. Extending the protocol to bi- and tri-cyclic systems was possible, as observed in the cases of 1-indanone (**21**), 9*H*-fluoren-9-one (**22**), 9*H*-thioxanthen-9-one (**23**) and (the more elaborated) fluoro-substituted

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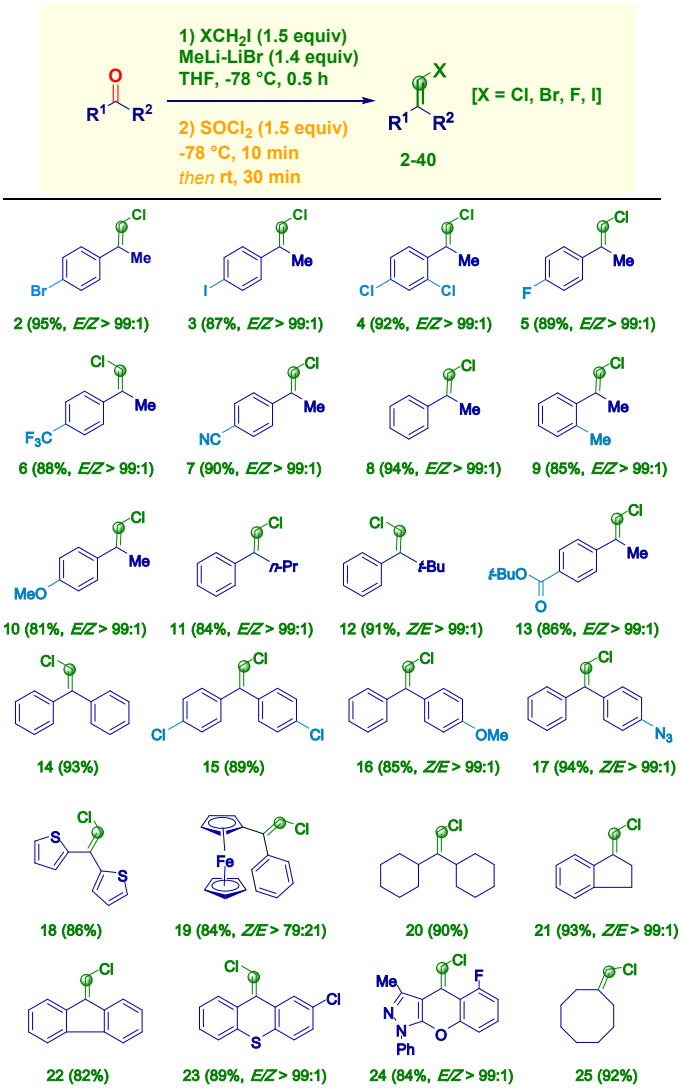
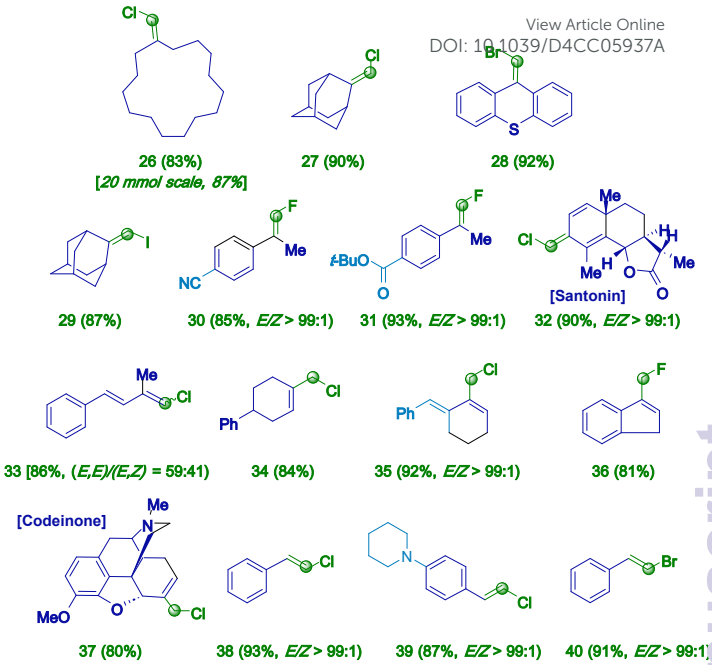
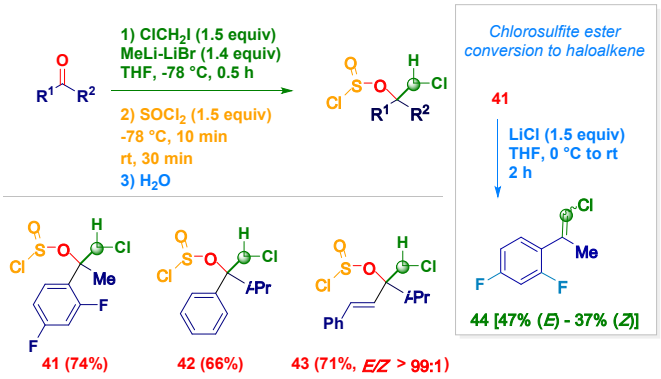
chromeno[2,3-c]pyrazol-4(1*H*)-one (**24**). Pure carbocyclic analogues including octan-1-one (**25**) and the expanded 15-membered ketone (**26**) gave the trisubstituted alkenes in high yield (also when scaling up to 20mmol), as well as, the sterically hindered adamant-1-one (**27**). The chemoselective methodology was not restricted to the use of $LiCH_2Cl$ as the C1-donor but was also applicable to the preparation of bromo- (**28**) iodo- (**29**) and fluoro- (**30**-**31**) olefins with $LiCH_2Br$,[18] $LiCH_2I$[19] and $LiCH_2F$[20] respectively, thus showing a remarkable synthetic versatility. Conjugated haloalkenes could be easily prepared in the cases of both cyclic (**32**) and acyclic (**33**) materials. It is interesting to highlight the success of the transformation conducted on the anthelmintic natural product Santonin (**32**) whose constitutive lactone moiety were inert under the reaction conditions. As a consequence of the higher thermodynamic stability of endocyclic double bonds (compared to exocyclic ones),[21] vinyl – allyl halide isomerization could take place, thus yielding structures **34**-**37** during the usual work-up. Again, the application of the method to the narcotic drug codeinone (**37**) further illustrates the significance of the protocol for the elaboration of medicinally relevant substances. Finally, the switching to aromatic aldehydes as electrophilic partners for carbenoids – *coeteris paribus* – provided a smooth route to β-halostyrenes (**38**-**40**), thus validating the protocol for the obtainment of (*E*)-haloalkenes.[22]





Scheme 2. Scope of the sequential carbonyl homologation / elimination *en route* to haloalkenes.

As mentioned in the optimization study (Table 1), by keeping temperature at -78 °C after the addition of $SOCl_2$, it was possible to unambiguously demonstrate the genesis of chlorosulfite esters, as the pertinent intermediates (Scheme 3). Notwithstanding, the subsequent treatment with a solution of LiCl in THF at room temperature, yielded the corresponding halo-alkene **44** albeit with poorer stereocontrol (presumably due to conducting the reaction at high temperatures).



Scheme 3. Trapping of chlorosulfite esters for mechanistic analysis.

In summary, we have reported an effective synthesis of trisubstituted halo-alkenes from ketones through a sequential homologation with lithium halocarbenoids ($LiCH_2Cl$, $LiCH_2Br$, $LiCH_2I$ and $LiCH_2F$ – generated from dihalomethanes and MeLi-LiBr under Barbier-type conditions at -78 °C), followed by a E2-type elimination triggered on the tetrahedral intermediate with thionyl chloride. The protocol exhibits a remarkable chemocontrol, as indicated by reacting ketones presenting a wide range of chemical functionalities (*e.g.* halogen, azido, nitrile, ferrocenyl, ether, ester, lactone, conjugated olefin, amine) which, in principle, may interfere with the carbenoids during the homologative event. Not only simple alkl-aryl

ketones are amenable for the process but, also (hetero)aryl-(hetero)aryl, (alkyl)-(alkyl) including macrocycles and a series of biologically active substrates featuring the ketone group could be equally employed. The application of the method to aromatic aldehydes furnishes β-halostyrenes, whereas aliphatic analogues are currently under investigations and results will be reported in due course.

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Data availability

The data supporting this article have been included as part of the ESI.

Conflict of interest

There are no conflicts to declare.

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Data Availability Statement

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The data supporting this article have been included as part of the Supplementary Information.