Bismuth(III) Halide-Catalyzed Tandem Aldol-Halogenation Reaction: A Convenient Synthesis of β-Halo Ketones and Esters[1]

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β-Halo carbonyl compounds, including β-halo acetals, are useful substrates in organic synthesis.[2] However, whereas the methods of synthesis of α-halo carbonyl compounds are numerous, it is apparently more difficult to obtain β-halo derivatives which suffer spontaneous dehydrohalogenation if the conditions are too drastic. The main processes used, with some limitations, are olefin acylation[3] and addition of hydrogen halides to α,β-unsaturated carbonyl compounds.[4] This latter reaction often leads to salts by protonation of the carbonyl oxygen, which then renders the carbon–carbon double bond unreactive toward hydrogen halide addition. The reaction of an enone with a tetraalkylammonium halide in anhydrous trifluoroacetic acid is an original and convenient synthesis for β-iodo ketones but remains less efficient for β-chloro ketones.[5]

Silicon reagents have also been used in the preparation of β-halo carbonyl compounds. Iodotrimethylsilane adds to α,β-unsaturated carbonyl compounds to give β-iodo carbonyl derivatives[6,7] or their acetals.[2g,h] The Mukaiyama reaction can lead to β-chloro ketones as unexpected side products.[8] However, when 2 equiv of $TiCl_4$ are used in the Mukaiyama procedure β-chloro acids and esters were obtained.[9] Some β-halo ketones have been obtained by direct coupling of a ketone with itself[10] or with benzaldehyde,[11] in the presence of a halosilane, by halogenation of silyl cyclopropyl ethers[12] and by other reactions involving organosilanes.[13,14] Aromatic β-fluoro esters were prepared by reaction between corresponding β-silyloxy esters and phenyltetrafluorophosphorane.[15]

The present paper describes tandem reactions in which the aldol condensation is coupled with the halogenation giving β-halo ketones and esters in high yield.

Table 1

R¹	R²	R³	A	R⁴	B	X	C
Ph	H	H	1	Ph	8	Cl	16
						Br	17
						I	18
Ph	H	H	1	ⁿPr	9	Cl	19
						Br	20
						I	21
2-furyl	H	H	2	Ph	10	Cl	22
						Br	23
						I	24
Et	Me	H	3	Ph	11	Cl	25
i-Pr	H	H	4ᵃ	Ph	12	Cl	26
i-Pr	Me	Me	5ᵃ	Ph	13	Cl	27
MeO	Ph	H	6	Ph	14	Cl	28
						Br	29
						I	30
MeO	Me	Me	7	2-furyl	15	Cl	31
						Br	32

ᵃ Isomeric purity: 80% (4), 95% (5).[16]

Results and Discussion

The starting carbonyl compounds, acetophenone, 2-acetylfuran, 3-pentanone, 3-methyl-2-butanone, 2,4-dimethyl-3-pentanone, methyl phenylacetate, and methyl isobutyrate, were converted to the corresponding enoxysilane A (1–7) (Table 1) by conventional methods.[16,17] The aldol reaction with the aldehyde R⁴CHO was carried out in the presence of the catalyst $BiCl_3$–$1.5ZnI_2$ that we have recently used for this type of reaction.[18,19] The O-silylated coupling ketol or hydroxy esters B (8–15) was isolated as previously described[18,19] and treated with 1 equiv of halotrimethylsilane TMSX (X = Cl, Br, I) (Scheme 1).

Although TMSBr does not react with simple alkoxysilanes,[20] the bromination of β-silyloxy ketones 8–10 by this bromosilane occurs readily at room temperature in dichloromethane to produce β-bromo ketones 17, 20, and 23. The iodination of the same compounds 8–10 by TMSI, prepared in situ by the exchange reaction between TMSCl and NaI in acetonitrile,[21,22] led to β-iodinated derivatives 18, 21, and 24. This reaction was faster than the iodination of simple alkoxysilanes.[20,22]

On the other hand, we observed that TMSCl does not yield chlorides under the same conditions. However, to our surprise, chlorination of 8–10 occurred readily when $BiCl_3$ was used as catalyst. These conditions were also successful on β-silyloxy ketones 11–13. This result seemed

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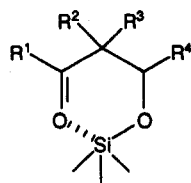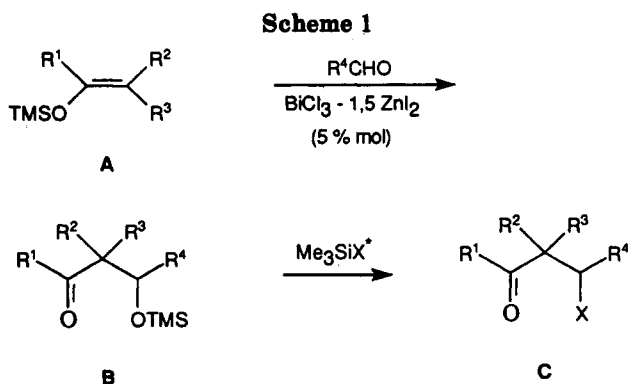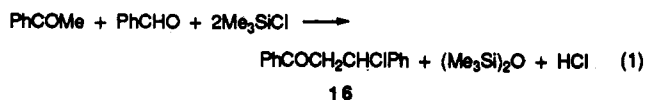
Figure 1.

Scheme 1

(*) X = Cl (BiCl₃, 5 % mol), Br, I

interesting to us in so far as the substitution of a silyloxy group bonded to a carbon atom by a chlorine atom (ROSi → RCl) is only possible at elevated temperatures using polychlorosilanes.[23,24] Although selenium dioxide is known to convert TMSCl into a strong chlorination reagent of alcohols, this catalyst does not assist the conversion of alkoxysilanes to chlorides.[25] Consequently, we have shown for the first time that *bismuth(III) chloride activates the silicon–chlorine bond*, ultimately leading to the cleavage of the carbon–oxygen bond in alkoxysilanes. We observed that these results are not isolated examples and that chlorosilanes (mono- and polychlorosilanes) are able to participate in chlorination reactions, in particular of *alcohols*, in the presence of a catalytic amounts of BiCl₃, which proves to be a better catalyst than other Lewis acids (such as ZnCl₂) for this Si–Cl activation.

As with TMSBr and TMSI, the above chlorination reaction proceeds more readily with the β-silyloxy ketones 8–13 than with alkoxysilanes of the type RCHOTMSR′ which are chlorinated by TMSCl (BiCl₃) at higher temperatures.[26] This enhancement of reactivity could arise from an anchimeric assistance in which coordination of silicon with the oxygen of the carbonyl group (Figure 1) would weaken the carbon–oxygen bond β to silicon, facilitating C–OSi → C–X substitution. In this regard, we have observed that the chlorination of ketol PhCOCH₂-CHOHPh by TMSCl, 5% BiCl₃ does not take place under the same conditions, whereas the corresponding silylated derivative 8 was very easily chlorinated.

It is known that TMSI reacts with the ester function.[21,27] This could appear as a limitation to the extension of the earlier tandem reaction for the synthesis of β-halo esters. However, some examples reported in Scheme 1 (Table 1, products 28–32) show that the C–O(Si) bond was more

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PhCOMe + PhCHO + 2Me₃SiCl ⟶

PhCOCH₂CHClPh + (Me₃Si)₂O + HCl   (1)

16

ᵃ Key: rt; solvent, CH₂Cl₂; catalyst, BiCl₃ (5% mol); 85% yield after 6 days.

easily cleaved than the C–O(Me) bond of the ester function by the three halosilanes. This result can also be explained by an anchimeric effect (Figure 1).

To investigate possible stereoselectivity in the halogenation reaction, we attempted the chlorination (TMSCl, 10% BiCl₃) of ethyl 3-[(trimethylsilyl)oxy]butyrate of which both enantiomeric forms are available. The chlorination of this β-aliphatic ester did not occur, in contrast with those of β-aromatic esters 14 and 15. This limitation does not exist with ketones since the β-aliphatic ketone 9 was halogenated as well as the β-aromatic one 8. The two diastereomers of 14, 14a (44%) and 14b (56%), were separated, and each was separately chlorinated (TMSCl, 5% BiCl₃). Both diastereomers gave the same major diastereomer of 28, although in somewhat different ratios (28a/28b = 95/5 and 62/38 from 14a and 14b, respectively), thus exhibiting the nonspecific nature of the reaction. Our recent results on the chlorination of other oxygenated organic functions by TMSCl (BiCl₃)[26] corroborate this stereochemistry.

Another feature worth noting is that some of these tandem reactions can be carried out by a one-pot procedure; this is the case of the chlorination reaction giving the derivative 16. However, yields and purity of products were always higher after isolation of the intermediate B.

Concerning the derivative 16, it was also prepared by the reaction between acetophenone, benzaldehyde, and 2 equiv of TMSCl, in the presence of 5% BiCl₃ (eq 1, Scheme 2). However, this reaction was very slow and limited as the product 19 could not be obtained in the same way. In that respect, the catalytic power of BiCl₃ is higher than that of ZnCl₂, which does not catalyze this reaction (eq 1), considering that 0.7 equiv of ZnCl₂ gave only 44% of conversion.[12]

Conclusion

The isolation of the O-silylated intermediate of the Bi-(III)-catalyzed Mukaiyama–aldol reaction allows tandem aldol-halogenation reactions which were previously unknown.[28]

In the course of this study, an activation of the silicon-chlorine bond of the chlorotrimethylsilane by bismuth-(III) chloride had been observed. To our knowledge, this is the first proven example of activation of a chlorosilane by a Bi(III) salt. After recent results concerning the Mukaiyama–aldol and –Michael reactions[18,19,29] this activation extends the potential of these new catalysts which we are further developing in our laboratory.

Experimental Section

General. For general experimental and analytical information see previous papers.[18b,19]

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Silyl enol ethers 1–3, 4 (isomeric purity 80%), 5, and silyl ketene acetals 6 and 7 were prepared by a conventional method.[16,17] For aldol condensations (A → B) we have used previously described experimental procedures [8, 9, 11 (52/48 diastereomeric mixture), 12, 13,[18] 10, 14 (56/44 diastereomeric mixture) and 15[19]].

Typical Procedure. A mixture of 10 mmol of β-silyloxy carbonyl compound B in 10 mL of dry dichloromethane and 158 mg (0.5 mmol) of anhydrous bismuth trichloride was stirred under nitrogen during the addition of 1.4 mL (11 mmol) of chlorotrimethylsilane. The reaction was monitored by ^{1}H-NMR [TMSCl → (TMS)$_2$O]. After addition of 20 mL of an aqueous saturated solution of sodium bicarbonate and extraction with 3 × 10 mL of CH$_2$Cl$_2$, the organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product thus obtained was analyzed by ^{1}H-NMR and then recrystallized or flash chromatographed on silica gel (Merck 60).

The β-bromo carbonyl compounds were prepared by a similar procedure without catalyst using bromotrimethylsilane in dichloromethane, except in the case of 29 for which a catalytic amount of BiCl$_3$ was required to obtain a high yield.

For the synthesis of β-iodo carbonyl compounds, iodotrimethylsilane (11 mmol) was prepared from chlorotrimethylsilane and sodium iodide in acetonitrile (10 mL).[22,23] To this solution was added 10 mmol of compound B in 10 mL of acetonitrile by syringe. The reaction was monitored as before. After workup (aqueous sodium bicarbonate) and extractions (CH$_2$Cl$_2$), the organic layer was treated by aqueous saturated sodium thiosulfate, washed with H$_2$O, dried over sodium sulfate, concentrated under reduced pressure, and finally analyzed and treated as above.

The NMR yields from the crude products were ≥88%, but all products are relatively stable and prolonged heating in the recrystallization solvent or chromatography on silica gel cause, in some cases, partial decomposition of the product by elimination of HX. Products 16–18, 22–24, 28, and 29 were purified by recrystallization (68–75% isolated yield), and product 19 was prepared by chromatography on silica gel (82% isolated yield).

Supplementary Material Available: Experimental data and ^{1}H, ^{13}C NMR and IR spectra for compounds 16–32 (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.