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BiX_3 as an Efficient and Selective Reagent for the Halogen Exchange Reaction

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Abstract

Bismuth halides are efficient and selective reagents in the halogen exchange reactions carried out under mild conditions. This rapid, high yield reaction proceeds mainly with retention of configuration.

Keywords: Bismuth; halides; halogenation; exchange reactions.

The great synthetic potential of organic halides puts them in a unique position within organic chemistry. Organic halides play a key role in much of contemporary organic synthesis. The most common precursors to alkyl halides are alcohols; their conversion into halides is one of the most frequently used functional group transformation reaction.[1]

In the course of our ongoing research on the bismuth(III) derivatives used as reagents in halogenation reactions[2], we have recently found a new $BiCl_3$-chlorinating reaction which provides chlorides from secondary and tertiary alcohols.[3] Moreover, organic transformations based on bismuth reagents have proven to be of synthetic utility.[4]

The halide exchange reaction between alkyl halides and various halides salts, known as the Finkelstein reaction[5], and the more recent transhalogenation reaction[6] between pairs of alkyl halides are two processes usually involved for the preparation of alkyl halides. However, in both cases the formation of undesired side products due to elimination reactions limits the synthetic utility of these methods. The search for alternative efficient processes constitutes a topic of constant interest.[7]

Results and Discussion

We recently observed that $BiCl_3$ could constitute an efficacious reagent for the transhalogenation of alkyl halides[3]. Our new approach to this classic problem involves the use of BiX_3 derivatives in 1,2-dichloroethane (DCE); it is a simple and effective procedure.

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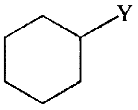
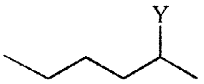
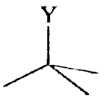
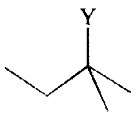
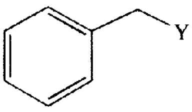
To our knowledge, this is the first example of the use of BiX_3 to promote halogen exchange. In this report, we underline the interest of this new innovative halogen exchange reaction represented by the following general scheme.

$$R\text{-}Y + BiX_3 \longrightarrow R\text{-}X \quad \text{with} \quad \begin{cases} Y = I \text{ and } X = Br \text{ or } Cl \\ Y = Br \text{ and } X = Cl \end{cases}$$

To establish the scope and limitations of the halogen exchange reaction with Bi(III) halides , we extended our preliminary study to the reactivity of a series of diverse alkyl halides (RY) in the presence of BiX_3. The progress of the reaction was monitored by GC. A variety of structurally diverse alkyl halides was examined. The results are summarized in Table 1.

Table 1. Halogen exchange reactions between alkyl halides and BiX_3.

Entry	R – Y	Y	BiX_3	T°C[b]	Reaction times	Conversion %
1		I	$BiBr_3$	reflux	8 days	7
		I	$BiCl_3$		"	7
		Br	$BiCl_3$		"	3
2		I	$BiBr_3$	reflux	1h30	100
		I	$BiCl_3$		15 min	100 (98)[a]
		Br	$BiCl_3$		30 min	100
3		I	$BiBr_3$	reflux	1h30	100
		I	$BiCl_3$		30 min	100
		Br	$BiCl_3$		1h00	100
4		I	$BiBr_3$	25°C	1h45	100 (98)[a,c]
		I	$BiCl_3$		4h00	100
		Br	$BiCl_3$		50 min	100
5		I	$BiBr_3$	25°C	5 min	100
		I	$BiCl_3$		5 min	100
		Br	$BiCl_3$		30 min	100
6		I	$BiBr_3$	reflux	1h45	100 (94)[a,c]
		I	$BiCl_3$		1h15	100
		Br	$BiCl_3$		2h30	100
7		I	$BiBr_3$	25°C	2h15	100 (97)[a]
		I	$BiCl_3$		1h30	100
		Br	$BiCl_3$		2h30	100

[a] Isolated yield of pure product, as determined by GC, exhibiting ^1H NMR data consistent with their assigned structures.
[b] 1,2- dichloroethane. [c] In dichloromethane.

From Table 1, it is worthwhile pointing out the following observations:
i) a variety of secondary or tertiary alkyl iodides and bromides are rapidly and quantitatively converted into the corresponding chlorides or/and bromides by exposure to $BiCl_3$ or $BiBr_3$ in DCE. Benzylic and allylic analogues show the same behaviour. In contrast, primary halides exhibited a very low reactivity (entry 1). The last observation agrees with that previously reported in the chlorination reaction of alcohols with $BiCl_3$[3]. This study shows clearly that $BiCl_3$ allows the displacement of an iodine (bromine) atom by chloride. In the same way $BiBr_3$ permits the substitution of an iodine atom by bromide. A characteristic colour change from white ($BiCl_3$) to yellow (like $BiBr_3$) takes place during this Br/Cl exchange reaction; similarly the colour changed from yellow ($BiBr_3$) to purple (like BiI_3) for the I/Br exchange.

ii) the results generally indicate that quantitative conversions could be attained with one molar equivalent of BiX_3. Halogen exchange reactions can be achieved with reaction times ranging from 5 min to 4 h without detecting any byproducts or rearranged products.
The same study realized with 1/3 molar equivalent of BiX_3 with some alkyl halides led to same conversion rates but with longer reaction times.

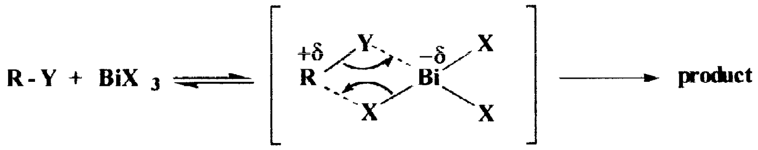
iii) the tertiary alkyl halides (entries 4 and 5) seem to be the most reactive substrates towards BiX_3 and whatever the considered halogen exchange.

iv) Moreover, we have to mention that the opposite halide exchanges, i.e. Br/I, Cl/I (with BiI_3), or Cl/Br (with $BiBr_3$) were not detected under the similar conditions. This result can be explained by the Hard and Soft Acids and Bases concept[8] (HSAB principle) in organic chemistry: soft acids prefer to bond to soft bases. The Bi_3^+ ion is considered as a soft (or eventually borderline) acid and should prefer to bond to soft bases like I^- rather than with Br^- (borderline base) and even less with an hard base such as Cl^-.

Results obtained in such halogen exchange reactions displayed prominently two important and general features:

- according to entries 3 and 5, the alkyl halide produced (RX) in the reactions seem to indicate no rearrangement were involved.
- no alkenes were detected contrary to that described for the halogenation reaction of alcohols with $BiCl_3$[3].

The mechanism shown on the scheme 1 appears to be in accord with these observations and is more likely to involve a 4-centre transition state than formation of an ion-pair $R^+/YBiX_3^-$ because of the low polarity of the solvent.

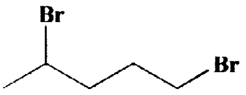
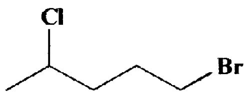
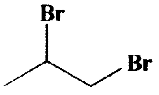
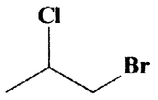
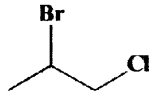
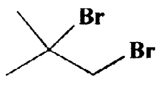
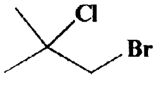


Scheme 1

The stereochemistry of the halogen exchange reactions was investigated using the neomenthyl bromide[9] which was converted by $BiCl_3$ for 2h at reflux (DCE) to a mixture of neomenthyl and menthyl chlorides[10] in a ratio of 85: 15 ($[\alpha]_D = + 40.8°$, c = 1.40, ethanol)[12]. These findings will suggest that in the halogen exchange reaction, the bismuth chloride attacked the neomenthyl bromide mainly in an SN_i mechanism which agrees with the four center reaction mechanism proposed above. The menthyl chloride was obtained from the incursion of a small competing inversion process. The menthyl chloride formation confirms the lack of rearrangement in those reactions.

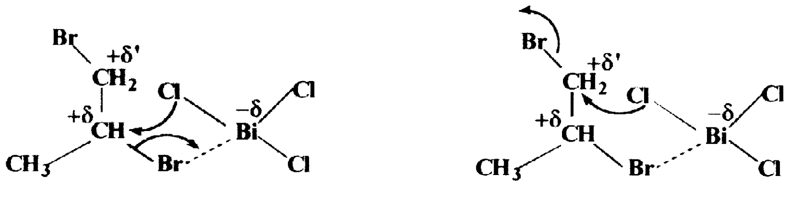
Finally, we postulated that this new BiX_3 transhalogenating system should exhibit an interesting functional group selectivity. As primary substrates react very slowly in the presence of BiX_3, a selective exchange was expected with dihalides, primary/secondary or primary/tertiary. To take advantage of this selectivity, this halogen exchange reaction was extended to the chlorination of three dibromides respectively 1,4-dibromopentane I, 1,2-dibromopropane II and 1,2-dibromo-2-methylpropane III, with $BiCl_3$. Their conversions afforded the results reported on Table 2.

Table 2. Selective halogen exchange reactions between alkyl dibromides and $BiCl_3$.

Dihalides		T°C	Reaction times	Conversion %	products
	I	reflux	1h	100	
	II	reflux	24h	100	 IIa 75%  IIb25%
	III	25°C	9h	100	

Results with I and III are consistent with our preliminary statements. We observed a total selectivity; thus, those dibromides were totally converted to afford only the corresponding chloride in secondary and tertiary positions respectively. However, if I presents a reaction time comparable to that of the preceeding reaction (Table 1, entry 3), the tertiary bromide III required a longer reaction time (9 h) than those already mentioned with brominated tertiary derivatives (entries 4 and 5; 30 to 50 min). Besides, compound II showed a quite surprising behaviour since it gave rise both to the expected chloride IIa (75%) in addition to the unexpected product (25%) arising from the exchange of the primary bromine atom without going as far as the 1,2-dichloride derivative. This abnormal behaviour seems to indicate that the proximity of two bromine atoms can also play an important role as also shown by the longer reaction times.

Actually the presence of the unexpected IIb can reasonably be interpreted at least in part by consideration of such factors as the inductive effect of the neighbouring bromine and the acceptor properties of BiX_3. Thus, in compound II, the bromine atom on the methine carbon presents a negative inductive effect certainly enhanced by the complexation with $BiCl_3$ which should weaken the CH_2-Br bond permitting the primary bromine displacement by the chlorine atom situated in the proximity (scheme 2).



Scheme 2

Those two competitive reactions due to the proximity of two bromine atoms could also explain longer reaction times compared to results observed in the Table 1.

Conclusion

In summary the easy workup of the reaction mixture entails only the removal of the inorganic solid remaining by filtration. The simplicity and the selectivity of this procedure and its rapidity under mild conditions recommend it as a method of choice for the transhalogenation reactions. However, the role and the mechanism of the noteworthy activity of BiX_3 is still not completely understood. Further investigations in these area are now underway.

Experimental

Dichloroethane was distilled from calcium hydride. ^1H NMR spectra were recorded in a Brucker ACE-250 apparatus at 250 MHz with $CHCl_3$ as an internal reference in $CDCl_3$ solutions. GC analysis were performed with a Delsi 330 apparatus. Optical rotations were measured using a Perkin Elmer 241 polarimeter with specific rotations determined at 20°C.

General procedure for halogen exchange reactions:

Anhydrous DCE (5ml) was stirred in the presence of BiX_3 (1 eq.) at reflux (unless stated otherwise) followed by the addition of the halide; RY (1 eq.). The reaction was followed by GC until complete consumption of the substrate. The reaction mixture was filtered and solvent evaporation led to products. The products were analyzed by GC, ^1H NMR and GC-MS and their spectral data compared to those of authentic samples.

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14. Optical rotation measured from commercially available menthyl chloride (Sigma-Aldrich) ($[\alpha]_D = -52.4°$, neat).