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From Azides to Nitriles. A Novel Fast Transformation Made Possible by BrF_3

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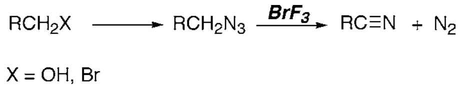
ABSTRACT



$$RCH_2X \longrightarrow RCH_2N_3 \xrightarrow{BrF_3} RC{\equiv}N + N_2$$

X = OH, Br

Various alkyl and aryl azides, readily obtained from halides or alcohols, were transformed into the corresponding nitriles using bromine trifluoride in moderate to good yields. The reaction is general and gives positive results with aliphatic, aromatic, cyclic, and functionalized azides. It can also be applied to the synthesis of optically active nitriles.

For a long time, nitriles have been recognized as efficient starting materials for the preparation of amines, ketones, heterocycles, and other families of compounds.[1] Usually, they can be obtained by dehydration of amides or through nucleophilic reactions with the cyanide ion. While these methods are very useful, other methods involving readily accessible starting materials such as alkyl halides or alcohols that can be converted to nitriles without carbon chain elongation are needed. The commonly used syntheses also employ harsh conditions leading to byproducts derived from eliminations and rearrangements and, in some cases, to racemization.

Azides, as Professor Sharpless, the 2001 Nobel Laureate, put it, "make fleeting appearance in organic synthesis" mainly because of "irrational fear".[2] For more than 50 years, such fears and prejudice were, and occasionally still are, responsible for the fact that bromine trifluoride (BrF_3) is a reagent that organic chemists have been avoiding. Recently, we described a new chemistry of azides transforming them to nitro compounds with $HOF{\cdot}CH_3CN$, a reagent derived directly from F_2.[3] We report here the reaction of azides with BrF_3[4] resulting in quite useful and novel syntheses of a variety of nitriles without incorporation of of fluorine and bromine atoms.

Our experience indicates that like F_2, bromine trifluoride, despite its strong reactivity, can under the appropriate conditions be a remarkably selective reagent. One of these conditions that has to be fulfilled calls for the soft acidic bromine to complex a soft basic atom such as nitrogen or sulfur in the reactant, bringing the reactive naked fluorine in the vicinity of the reaction center.[5] This enabled us to synthesize various alkyltrifluoromethyls,[6] aryltrifluoromethyls,[7] trifluoromethyl ethers,[8] α-trifluoromethyl acids,[9] CHF_2[10] moiety, β,β-difluoroacrylates,[11] and other families of compounds.[12] The basic nitrogen atoms in azides offer such an anchor, and it was of interest to explore the results of such coordination between BrF_3 and the N_3 group. We were pleased to find that, within a few seconds, BrF_3 successfully

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* Fax: 972-3-6409293.

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[4] BrF_3 is commercially available from Air Products, Ozark Fluorine Specialties, and probably other companies around the world. We prepare our own BrF_3 by passing 0.58 mol of pure fluorine through 0.2 mol of bromine placed in a copper reactor at 0−10 °C. When no excess of bromine is present, the BrF_3 obtained is an indefinitely stable pale yellow liquid and has a density of 2.5 with a mp of 7−9 °C; see also: Simons, J. H. *Inorg. Synth*. **1950**, *3*, 184. Stein, L. *J. Am. Chem. Soc.* **1959**, *81*, 1269.

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[12] See, for example: Rozen, S.; Ben-David, I. *J. Org. Chem.* **2002**, *67*, 8430.

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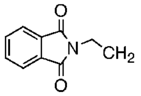
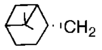
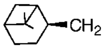
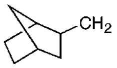
transformed primary and secondary methylene azides to the corresponding nitriles without altering the skeleton of the molecule or racemizing chiral centers.

Following a known procedure,[13] 1-azidodecane (**1a**) was easily prepared from bromodecane and sodium azide in excellent yield. Treating **1a** with BrF_3 gave decanenitrile (**2a**)[14] in 60% yield (Table 1).

Table 1. Preparation of Alkyl Nitriles

$$\underset{\mathbf{1}}{RCH_2N_3} \xrightarrow{BrF_3} \underset{\mathbf{2}}{RC\equiv N} + N_2$$

Compound	R group	yield
a	$R = CH_3(CH_2)_7CH_2$	60%
b	$R =$ *cyclo*-$C_6H_{11}(CH_2)_2$	60%
c	$R =$ *cyclo*-C_6H_{11}	45%
d	$R = ClCH_2(CH_2)_3CH_2$	60%
e	$R =$ *p*-$NO_2C_6H_4$	40%
f	R = 	40%
g	RCH_2 = 	30%
h	RCH_2 = 	30%
i	R = 	55%
j	R = $MeOOC{-}(CH_2)_4$	30%
k	R = $MeCO{-}(CH_2)_3$	traces

Bromine trifluoride is able, in certain cases, to substitute tertiary hydrogens similar to F_2.[15] The reaction with the azide moiety, however, proceeded much faster, and as a result, 3-cyclohexylpropyl azide (**1b**) was converted to 3-cyclohexylpropionitrile (**2b**) in 60% yield.[16] Secondary methylene azides such as cyclohexylmethyl azide (**1c**) also react rapidly with BrF_3 to produce cyclohexanecarbonitrile (**2c**),[17] although in a slightly reduced yield of 45%. Bromine trifluoride is also capable of substituting chlorine atoms by fluorine atoms as it was demonstrated by the synthesis of the fluorinated anesthetic, desflurane.[18] However, we found that the present reaction will tolerate chlorine in the reactant since BrF_3 reacts with the azido moiety much faster than the substitution of the chlorine atom. Indeed, 1-azido-6-chlorohexane (**1d**) was reacted with bromine trifluoride to give 6-chlorohexanitrile (**2d**) in 60%.[19]

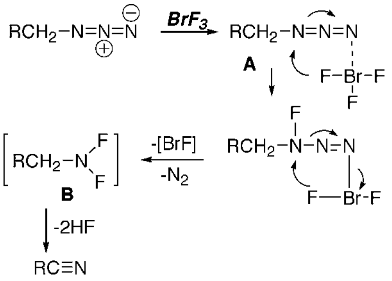
BrF_3 can act as a brominating reagent for aromatic compounds.[20] Still, with deactivated aromatic derivatives, bromination is slower than the reaction with the azide. *p*-Nitrobenzyl azide (**1e**) and *N*-(3-azidopropyl)phthalimide (**1f**) were reacted with bromine trifluoride to form *p*-nitrobenzonitrile (**2e**)[21] and *N*-(3-cyanoethyl)phthalimide (**2f**)[22] in 40% yields without altering the original aromatic ring.

The preparation of optically active nitriles in general is not a trivial task. Racemization either in the starting materials or products is very likely under conditions needed for substitution or dehydratation reactions. This prompted us to examine the synthesis of chiral nitriles using BrF_3. Compounds **1g** and **1h**, for example, were prepared from (1*S*,2*R*,5*S*)-(−)-myrtanol and (1*S*,2*S*,5*S*)-(−)-myrtanol in good yields following known procedures.[23] Their fast reaction with BrF_3 at 0 °C gave (1*S*,2*R*,5*S*)-2-cyano-6,6-dimethylbicyclo[3.1.1]heptane (**2g**) and (1*S*,2*S*,5*S*)-2-cyano-6,6-dimethylbicyclo[3.1.1]heptane (**2h**),[24] respectively, with retention of configuration and in 30% yield. The relatively low yield in these cases is due to our inability to completely prevent fragmentations and rearrangements of the sensitive myrtanyl skeleton under acidic conditions. The yield was improved when BrF_3 was brought in contact with bicyclic compounds possessing less sensitive skeletons such as 2-(2′-bornyl)ethyl azide (**1i**), which resulted in the corresponding nitrile **2i**[25] in 55% yield.

With compounds possessing a carbonyl group, the results were less impressive, as methyl 5-cyanopentonate (**2j**)[26] was obtained in only 30% yield when **1j** was reacted with bromine trifluoride. The yields were even lower with ketones and particularly with azidohexan-5-one (**1k**), as only traces of the corresponding nitrile **2k** were observed. Apparently, the enol form of the carbonyl is very reactive with the reagent, leading eventually to tars.

Similarly to the oxidation of azides by $HOF{\cdot}CH_3CN$,[3] the first step in the transformation of azides to nitriles is the complexation of the electrophilic bromine in BrF_3 with the basic nitrogen atom of the azido group (**A** in Scheme 1). After loss of nitrogen and BrF, the unstable intermediate **B** is formed, which readily eliminates two molecules of HF to give the more thermodynamically stable nitriles (Scheme 1). Such elimination is not without precedent, as it was reported

Scheme 1. Preparation of Alkyl NitrilesFormation of Nitriles: Mechanism



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that even more stable derivatives such as RCF_2NH_2 readily eliminate two molecules of HF to produce the corresponding nitriles.[27] An alternative mechanism calls for abstraction of a proton from the CH_2 group by a basic fluoride, eventually forming a fluoroimine that then can lose HF and form the nitrile moiety. While there is not concrete evidence for either mechanism, we would like to point out that the fluorine atoms in BrF_3 are not very basic and can sometimes act even as electrophiles.[28] Furthermore, the T-geometry of BrF_3 makes a six-membered ring transition state quite unfavorable.

In conclusion, this work demonstrates a development of a novel synthetic method that converts several types of alkyl and aryl halides (or alcohols) to the corresponding nitriles, using the under-utilized azide group without altering the carbon chain or its configuration. It also adds yet another reaction to the already considerable number of processes, whose starting point is F_2, eventually forming fluorine-free products.[29] We hope that this work will encourage further unveiling of the synthetic potential of bromine trifluoride in organic chemistry.

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Supporting Information Available: Complete ^{1}H NMR, ^{13}C NMR, IR and microanalysis data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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