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A new efficient deprotection of azines, hydrazones and oximes. An excellent route for exchanging oxygen isotopes in carbonyls

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Abstract—Carbonyls, protected as azines or other C=N derivatives can be deprotected by $HOF{\cdot}CH_3CN$ in seconds to the corresponding ketone or aldehyde in very good yields. This reaction also offers a very efficient route for replacing the oxygen atom of most carbonyls with any other oxygen isotope, for example, [18]O.

1. Introduction

The notion of protecting various functional groups in a molecule is almost as old as organic chemistry itself. One of the conditions for a moiety to assume the role of protecting group has to be the ease and efficiency of its removal when its purpose has been fulfilled. When it comes to carbonyls there is practically one exclusive protective family consisting of various acetals and thioacetals. The first category is stable to bases but very sensitive to acids, a disadvantage if the protected compound has to encounter acidic media and an advantage since it is easy to remove.[1] Thioacetals are more stable in general, and hence have gained considerable popularity,[1,2] but their removal is more difficult. In both cases the protected products are rarely crystalline making their purification somewhat tedious.

In general, most types of azines, various hydrazones and oxime ethers are readily formed in excellent yields. Semicarbazones, hydrazones and alike are stable compounds and have had an important role in synthesis and analysis in addition to their frequent use as protecting groups.[1–3] With azines the situation is different and one can only occasionally find this group used for protecting carbonyls, mainly because the deprotection step is quite problematic.

In many cases azines are considered to be a synthetically 'dead end'. They are easily, and usually quantitatively, obtained from carbonyls and hydrazine hydrate forming stable derivatives. However, their resistance to conversion back to the original carbonyl compound has excluded them from being a popular strategy. There have been several attempts to decompose azines to the corresponding ketones or aldehydes, but prolonged reaction times (up to 3 days), high temperatures, polluting reagents based on heavy metals, inseparable mixtures and low yields, rendered these methods impractical.[4]

The $HOF{\cdot}CH_3CN$ complex is readily made by passing commercial dilute fluorine through aqueous acetonitrile. It is an excellent oxygen transfer agent,[5] which can oxidize alcohols, ketones[6] and ethers.[7] It is able to transform aliphatic and aromatic amines, including amino acids, into the corresponding nitro derivatives[8] and can hydroxylate sp^3 tertiary carbon centres.[9] This agent was also used for other oxygen transfer reactions such as epoxidation of olefins[10,11] and aromatic rings,[12] transforming azides and vicinal diamines into the corresponding nitro[13] and dinitro derivatives,[14] forming various N-oxides[15] and much more.[16] A few experiments convinced us that $HOF{\cdot}CH_3CN$ can be the reagent of choice for transferring oxygen to azines and other C=N containing compounds as well, regenerating the carbonyl moiety, with molecular nitrogen being the only noticeable by-product.

2. Discussion

Reacting adamantylazine (**1**) with a slight excess of $HOF{\cdot}CH_3CN$ at 0 °C for a few seconds produced adamantanone (**2**) in 98% yield. Parallel reactions with

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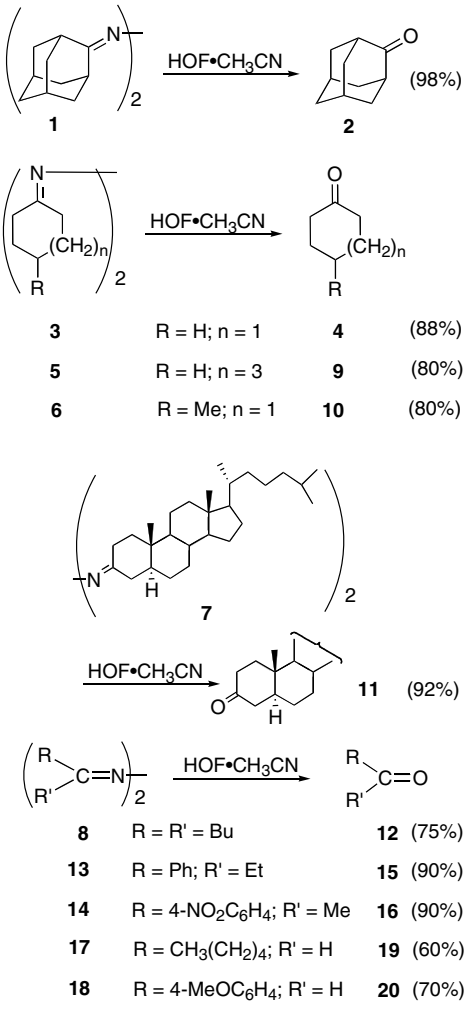
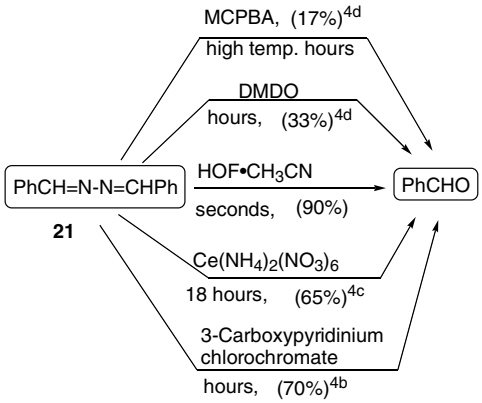
all the other azines tested by us, also proceeded with very good yields. Cyclic and straight chain ketones also underwent oxygen transfer, for example, cyclohexanone azine (**3**) was converted to cyclohexanone (**4**) in a few seconds and in 88% yield. Cyclooctanone azine (**5**), 4-methylcyclohexanone azine (**6**), cholestanone azine (**7**) and 5-nonanone azine (**8**), were all transformed to the corresponding ketones (**9**, **10**, **11** and **12**) in 80%, 80%, 92% and 75% yields, respectively (Scheme 1).

Potential complications may arise with aromatic azines, since HOF·CH_3CN is also capable of epoxidizing aromatic rings.[12] However, since the initial attack of the reagent on the carbon–nitrogen double bond is so fast, the aromatic ring remains intact as demonstrated by propiophenone (**15**) and 4-nitroacetophenone (**16**) which were obtained in a matter of seconds in excellent yields from their corresponding azines **13** and **14**. Aldehydes are of no exception, although special care has to be taken not to use a large excess of the reagent in order to avoid further oxidation to the corresponding acids. Hexylazine (**17**) and anisazine (**18**) were both reacted with HOF·CH_3CN for a few seconds at low temperature. Hexanal (**19**) and anisaldehyde (**20**) were obtained in 60% and 70% yields, respectively (Scheme 1).



Scheme 1. Deprotection of azines using the HOF·CH_3CN complex.



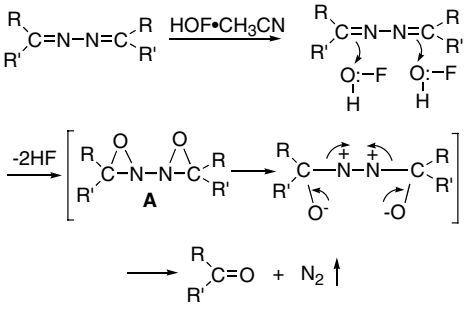
Scheme 2. From benzalazine to benzaldehyde using various oxidation agents.

It was of interest to compare carbonyl regeneration from the corresponding azines using some of the published methods. The following scheme, using benzalazine (**21**) as a model compound, depicts the differences (Scheme 2).

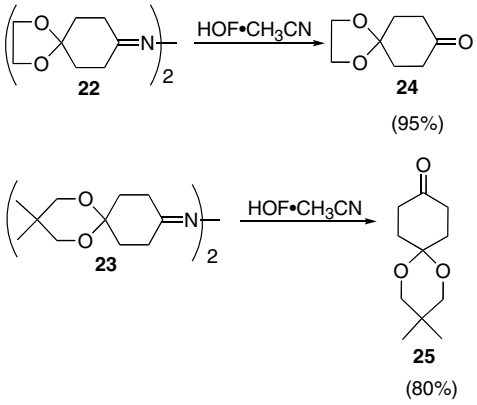
We believe that the reaction proceeds via initial attack of the electrophilic oxygen on the relatively electron rich double bond of the azine, resulting in the formation of the unstable bis-oxaziridine intermediate (**A**) and HF, the latter being the driving force of the whole process. The intermediate **A** may decompose via two consecutive N–O bond cleavages forming a ketone or an aldehyde along with nitrogen elimination (Scheme 3).

An especially interesting situation arises when more than one carbonyl group is found in a molecule. It is possible to protect one of them as a dimethyleneketal (e.g., **24**) or dimethyltrimethyleneketal (e.g., **25**) while the other carbonyl is protected as an azine (e.g., **22** and **23**). Despite the sensitivity of the ketals to acid, the azine group could be quickly and efficiently removed without affecting the ketal moieties, producing the mono protected diketones **24** and **25** in 95% and 80% yields (Scheme 4).

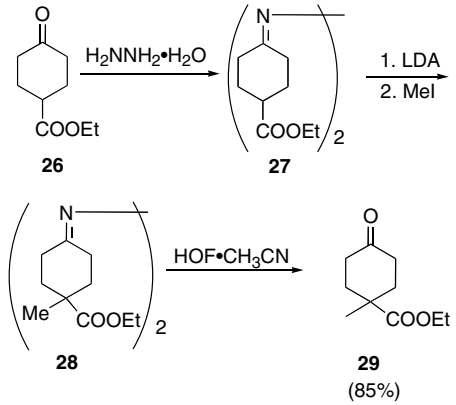
This behaviour offers an array of possibilities for differentiating two carbonyl groups for different reactions. An illuminating example is the alkylation of the ketoester ethyl 4-ketocyclohexanoate **26**. Although the four hydrogen atoms α to the ketone are more acidic than the single one α to the ester group, protecting the car-



Scheme 3. The proposed mechanism of azine deprotection.



Scheme 4. Selective azine deprotection.

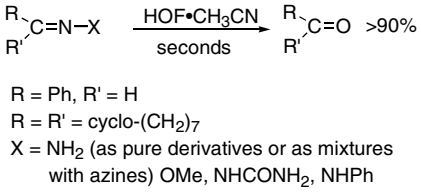


Scheme 5. Alkylation α to an ester in the presence of an α-keto moiety.

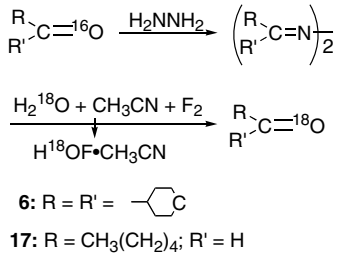
bonyl by forming the corresponding azine **27**, enabled us to abstract the α ester hydrogen using a strong base and alkylate the resulting anion with MeI. The stable new azine of ethyl 4-keto-1-methylcyclohexanoate (**28**) was rapidly deprotected using $HOF{\cdot}CH_3CN$ to give ethyl 4-keto-1-methylcyclohexanoate (**29**)[17] in 85% yield (from **26**) with no detectable amount of ester hydrolysis (Scheme 5).

Azine is not the only protecting group which could be readily removed by $HOF{\cdot}CH_3CN$. Practically any $R_2C{=}NR'$ moiety is suitable for this reaction. We treated hydrazones, methyl oxime ethers, semicarbazones and phenyl hydrazones with the acetonitrile complex of hypofluorous acid and obtained the corresponding carbonyls in yields of 90% and higher in a matter of a few seconds. These results help to circumvent an additional potential problem. Usually, when an azine is used as a protecting group, a small but noticeable amount of a hydrazone is also formed. Similarly, when a hydrazone is the desired derivative, formation of some azine is almost unavoidable. Usually, separation of these products is a time consuming process, but the present deprotection method does not require any separation, as it is equally effective for both types of compounds even as a mixture (Scheme 6).

One of the advantages of the $HOF{\cdot}CH_3CN$ complex is that the origin of its electrophilic oxygen is water, which



Scheme 6. Converting the C=N moiety to a carbonyl.



Scheme 7. Direct synthesis of a ketone and aldehyde containing the 18[O] isotope.

is the best source for all oxygen isotopes. Passing fluorine through acetonitrile and $H_2{}^{18}O$ produces $H^{18}OF{\cdot}CH_3CN$. When this reagent was reacted with either **6** or **17** the carboxylic oxygen atom in the corresponding product (**10** or **19**) was found to be the ^{18}O isotope (Scheme 7). The only other way to exchange oxygen isotopes in a carbonyl compound is to treat the molecule with an acid and a large excess of the very expensive $H_2{}^{18}O$. The HRMS (CI) of [18]O-4-methyl cyclohexanone (**10**-[18]O) and of [18]O-hexanal (**19**-[18]O) were recorded to be $m/z = 115.100769$, calcd for $C_7H_{12}{}^{18}O$ (M+1): 115.100885, and $m/z = 103.100535$, calcd for $C_6H_{12}{}^{18}O$ (M+1): 103.100885, respectively.

In conclusion, new possibilities for using azines, hydrazones and other C=N derivatives as protecting groups for carbonyl compounds have been described, since their removal with $HOF{\cdot}CH_3CN$ is very easy and efficient. This reagent also provides an excellent route for replacing a carbonyl oxygen with [18]O or any other oxygen isotope. It also should be stressed that the preparation of $HOF{\cdot}CH_3CN$ from dilute F_2 and water is as easy as turning a valve on and off (see also Ref. 15b). Today, working with dilute fluorine is not as exotic an adventure as it used to be 20 years ago and many laboratories have already used this element without any reported incidents. It is predicted that in 20 years every semiconductor and LCD plant, for example, will have its own F_2 generator.[18]

3. Experimental

For general procedures concerning working with fluorine, as well as for generating $HOF{\cdot}CH_3CN$ and working with it, see Ref. 15b. The physical and spectroscopic data for all final products are in perfect agreement with the proposed structures and were found to be identical to the respective authentic samples. For more details see also Supplementary data.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.090.

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