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2,2-Difluoro-1,3-dimethylimidazolidine (DFI). A new fluorinating agent†

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2,2-Difluoro-1,3-dimethylimidazolidine (DFI) is a new deoxo-fluorinating agent that is useful for the conversion of alcohols to monofluorides, and aldehydes/ketones to *gem*-difluorides under mild conditions.

Organofluorine compounds have received much attention due to their unique physical/chemical properties that may give rise to useful biological activities or novel characteristics. Deoxofluorination is one of the practical methods to prepare fluorine containing compounds; hydroxy groups can be converted to the corresponding fluorides, *e.g.*, alcohols to fluorides, carboxylic acids to carbonyl fluoride, aldehydes/ketones to *gem*-difluorides. In order to make it more useful, the fluorinating reaction should be highly selective and the agents should be easily handled. So far, in recent years, various deoxofluorinating agents have been developed to cope with these demands.

2-Chloro-1,1,2-trifluoroethyldiethylamine (Yarovenko agent),[1] and hexafluoropropyldiethylamine (Ishikawa agent)[2] have been demonstrated to convert alcohols to fluorides and carboxylic acids to carbonyl fluorides. However, these reagents do not normally react with aldehydes and ketones, and do not have enough stability on storage.

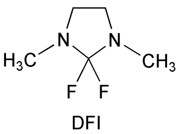
Diethylaminosulfur trifluoride (DAST) is known as an excellent fluorinating agent.[3] It is easily handled compared with other fluorinating agents such as HF and sulfur tetrafluoride, and is useful for replacing hydroxy group and carbonyl oxygens with fluorine under very mild conditions. However, the preparation of DAST, the reaction of highly reactive sulfur tetrafluorides with dimethylaminotrimethylsilane, requires special care at a low temperature. Thus, a specific manufacturing facility is required. As to safety, thermal decomposition has been reported at about 90 °C with gas evolution.[4] Bis(2-methoxyethyl)aminosulfur trifluoride(Deoxo-Fluor™)[5] is reported as a deoxofluorinating agent that is much more thermally stable than DAST and very effective alternative to DAST.

These fluorinating agents developed so far are effective for laboratory scale reactions but are not satisfactory for industrial practices. A fluorinating agent for oxygen-containing functional groups has not yet satisfactorily been developed for use in industry from the point of view of the preparation process, selectivity, yield, and economy.

Now, we report here a new fluorinating agent DFI that is applicable for the practical transformation of oxygen-containing functional groups to the corresponding fluorides. The fluorinating reaction requires no specific equipment or technique and can be carried out safely and with ease. The chemical properties of DFI are summarized in Table 1.

2,2-Difluoro-1,3-dimethylimidazolidine (DFI) is prepared by way of the halogen exchange reaction of 2-chloro-1,3-dimethylimidazolinium chloride (CDC) with spray-dried potassium fluoride (sd KF) in solvent, such as 1,3-dimethyl-2-imidazolidinone (DMI), acetonitrile, at 80–90 °C (Scheme 1). After filtration of the potassium chloride by-product and the potassium fluoride (used in excess for the halogen exchange reaction), DFI is easily isolated from the reaction mixture by distillation. DFI can be also used for the fluorinating reaction, without the need for isolation by distillation, in the solvent used for its preparation. CDC is prepared by the reaction of DMI with chlorinating reagents, such as phosgene, oxalyl chloride, in solvent.[6]

Table 1 Chemical properties of DFI **1**



DFI
1

Appearance	Clear liquid
Boiling Point	47 °C/37 mmHg
Melting Point	−8.7 °C
Density	1.096
Flash Point	40 °C
Exothermic starting point (ARC)	150.5 °C

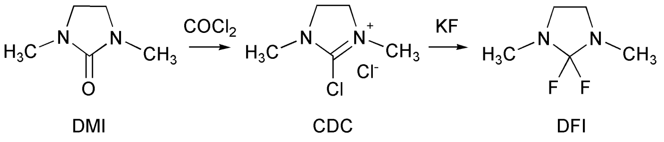
DFI can be stored, for example in PFA bottles at atmospheric pressure under inert gas. The thermal decomposition profile of DFI has been examined by accelerating rate calorimetry (ARC). Thermal decomposition begins at 150 °C. DFI is much more thermally stable than other typical deoxofluorinating agents, such as DAST and Deoxo-Fluor.

DFI has broad applicability for the preparation of organofluorine compounds. The fluorination of organic substrates with DFI is summarized in Table 2.

DFI reacts with primary alcohols, secondary alcohols and tertiary alcohols to afford alkyl fluorides in good yield under mild conditions.[7] In some cases, dehydrofluorinated products are obtained. The hydroxy groups of substituted phenol can be replaced with fluorine by DFI. For example, DFI reacts with 4-nitrophenol to afford 4-fluoronitrobenzene. However, fluorobenzene cannot be obtained by the reaction of DFI with phenol. In this case, the formation of 1,3-dimethyl-2-phenoxyimidazolinium hydrogenfluoride is observed.

DFI reacts with carboxylic acids to afford acyl fluorides under mild conditions in good yield. Conversion of carboxy group into a trifluoromethyl group is reported when benzoic acid is heated with DAST in the presence of sodium fluoride at 80 °C for 20 h.[3] However, the fluorination of benzoic acid with DFI does not give trifluoromethylbenzene under the same reaction conditions.

Reaction of aldehydes and ketones with DFI affords *gem*-difluoro compounds in moderate to high yields under mild conditions.[8] Side reactions, the formation of alkyl vinyl fluorides and alkyl acetylene, occur in the reaction of DFI with carbonyl compounds containing α-hydrogen. For example, DFI



Scheme 1 Preparation of DFI **1**.

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† Electronic supplementary information (ESI) available: experimental data. See http://www.rsc.org/suppdata/cc/b2/b204471d/

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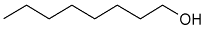
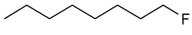
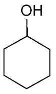
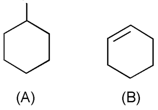
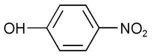
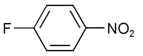
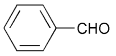
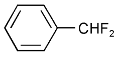
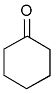
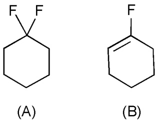
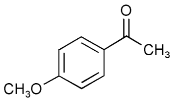
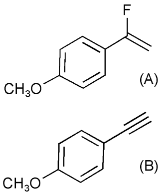
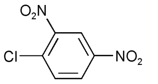
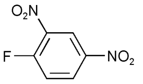
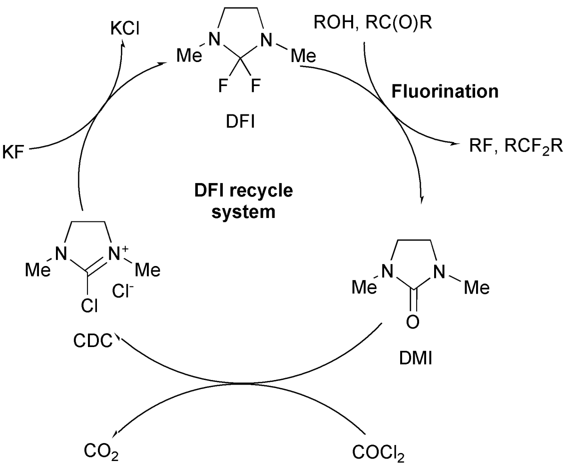
Table 2 Fluorination of model compounds with DFI **1**

Entry	Reactants	Conditions	Products	Yield (%)[a]
1		**1** (1.0 equiv.) Acetonitrile 25 °C, 1 h		87
2		**1** (1.0 equiv.) CH_2Cl_2 25 °C, 16 h		15 (A) 83 (B)
3		**1** (2.0 equiv.) Acetonitrile 85 °C, 15 h		62
4		**1**(1.6 equiv.) Acetonitrile 85°C, 8 h		82
5		**1** (2.0 equiv.) glyme 85 °C, 6 h		21 (A) 72 (B)
6		**1**(2.4 equiv.) Acetonitrile 85 °C, 8 h		15 (A) 85 (B)
7		**1** (2.0 equiv.) Acetonitrile 85 °C, 7 h		96

[a] Determined by gas chromatography.

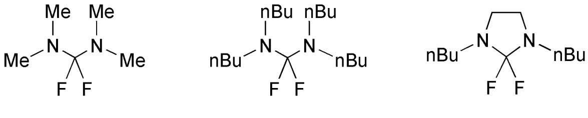
reacts with cyclohexanone to afford 1,1-difluorocyclohexanone and 1-fluorocyclohexene in the ratio of 23 : 77. If the desired products are *gem*-difluoro compounds, hydrogen fluoride is added to the reaction mixture to afford *gem*-difluoro compounds exclusively. DFI reacts with 4-alkoxyacetophenone to afford α-fluoro-4-methoxystyrene and 4-methoxyphenylacetylene in the ratio of 15 : 85. The mechanism of the formation of alkyl acetylene and alkyl vinyl fluorides has not yet been determined.

DFI can be recovered after the fluorinating reaction in the form of DMI, and this DMI can be reused for the raw materials of DFI. DMI can be recycled in the fluorinating reaction conducted by DFI. The recycling system of DMI in the fluorinating reaction by DFI is shown in Scheme 2. After the fluorinating reaction, DFI turns into DMI. Then CDC is prepared by the chlorinating reaction of DMI with a chlorinating agent, such as phosgene. And after that, DFI can be obtained by the halogen exchange reaction of CDC with spray dried KF. If the same solvent is to be used for the preparation of DFI and fluorination conducted by DFI, DFI need not to be isolated by distillation from the reaction mixture. So the preparation process of organofluorine compounds can become very simple. Other fluorinating agents, such as PPDA, DAST, Deoxo-Fluor cannot be recovered following the fluorinating reaction in the form of their raw materials. So from the economical and industrial point of view, fluorination by DFI is very useful for the preparation of organofluorine compounds.



Scheme 2 The recycling of DMI in the fluorinating reaction by DFI.

Several DFI analogues can be obtained by a synthetic method similar to that for DFI. First step, the preparation of tetraalkylchloroformamidinium chloride by the chlorinating reaction of tetraalkylurea with chlorinating agent, and second step, the preparation of bis(dialkylamino)difluoromethane which is a DFI analogue, by the halogen exchange reaction of tetraalkylchloroformamidinium chloride with spray dried KF. DFI analogues which we have already synthesized are, for example, bis(dimethylamino)difluoromethane (**2**), bis(di-n-butylamino)-difluoromethane (**3**), 1,3-di-n-butyl-2,2-difluoroimidazolidine (**4**) (Scheme 3). These DFI analogues are expected to have different chemical properties, such as reactivity, selectivity in the fluorinating reaction and thermal stability, in comparison with DFI. The fluorinating reaction of oxygen-containing functional groups conducted by these DFI analogues are now under investigation. We are now attempting to synthesize another DFI analogue and to investigate chemical properties.



2 **3** **4**

Scheme 3 DFI analogues.

In summary, we have developed a new fluorinating agent, DFI which is very effective for deoxo-fluorination reactions, much more thermally stable than other deoxo-fluorinating agents, and can be easily prepared and used in industry. Detailed studies of reactivity are now in progress.

Notes and references

† Electronic supplementary information (ESI) available: experimental data. See http://www.rsc.org/suppdata/cc/b2/b204471d/

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7 Typical procedure: DFI was added slowly to a solution of alcohol in an inert solvent in a nitrogen atmosphere at temperatures and for times indicated. The fluorinated products were isolated by pouring the reaction mixture into an aqueous solution of sodium carbonate, and then separating, drying, and distilling the organic layer.
8 Typical procedure is similar to that of fluorination of alcohols which is mentioned above. DFI was added slowly to a solution of carbonyl compounds in an inert solvent in a nitrogen atmosphere at temperatures and for times indicated. The fluorinated products were isolated by pouring the reaction mixture into an aqueous solution of sodium carbonate, and then separating, drying, and distilling the organic the organic layer.