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α,α-Difluorobenzylamines Deoxofluorination

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Introduction

α,α-Difluorobenzylamines are an important class of "N-CF_2R" type deoxofluorination reagents. Among various α,α-difluorobenzylamines with different substitution groups, α,α-difluorobenzyl (dimethyl)amine (DBDA) was first used for the deoxofluorination of simple alcohols and carboxylic acids [1]. However, the deoxofluorination property of DBDA has not been systematically studied, and the thermal stability of DBDA was also not shown. In 2004, *N,N*-Diethyl-α,α-difluoro(*meta*-methylbenzyl) amine (DFMBA) was first reported as a deoxofluorination reagent by Hara and coworkers [2]. In the next few years, the deoxofluorination property of DFMBA was well studied. DFMBA is a commercially available colorless liquid with boiling point of 81–83 °C/4 mmHg. Accelerating rate calorimetry analysis (ARC) showed that it is stable at temperatures up to 180 °C and decomposes gradually at 210 °C [3]. However, DFMBA can be destroyed gradually by moisture in air; thus, it must be stored in the refrigerator under inert atmosphere. Among a series of α,α-difluorobenzylamine reagents, only DFMBA has been commercialized probably due to the ready availability of its starting material, *N*,*N*-diethyl-*meta*-toluamide (DEET), which is a widely used pesticide. Another reason may be its higher hydrophobicity than nonsubstituted α,α-difluorobenzylamines, which can slow down the hydrolysis by water.

Preparation of Difluorobenzylamines

DBDA was first prepared from *N,N*-dimethylbenzamide with SF_4; however, only 17% yield was obtained due to the cleavage of C(O)-N bond caused by trace amounts of HF (Scheme 1, Eq. 1) [4]. Dmowski and Kamiński found that when KF was added to the reaction mixture to neutralize HF, the C(O)–N bond

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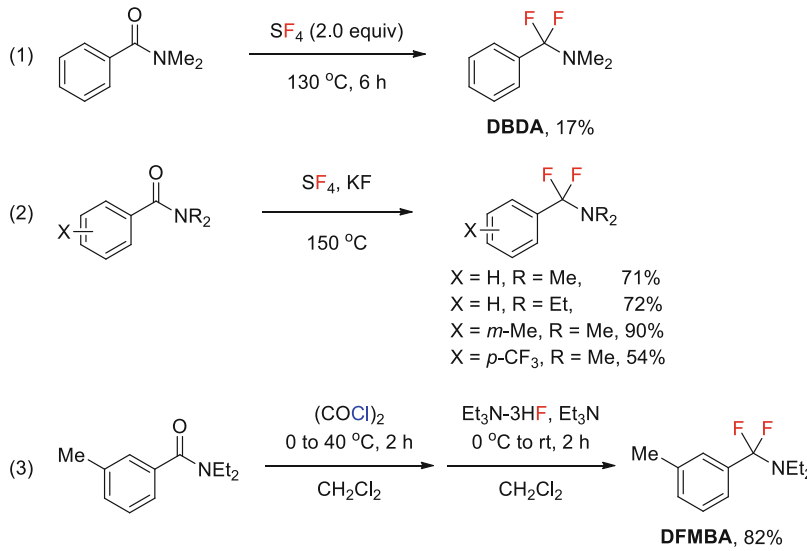


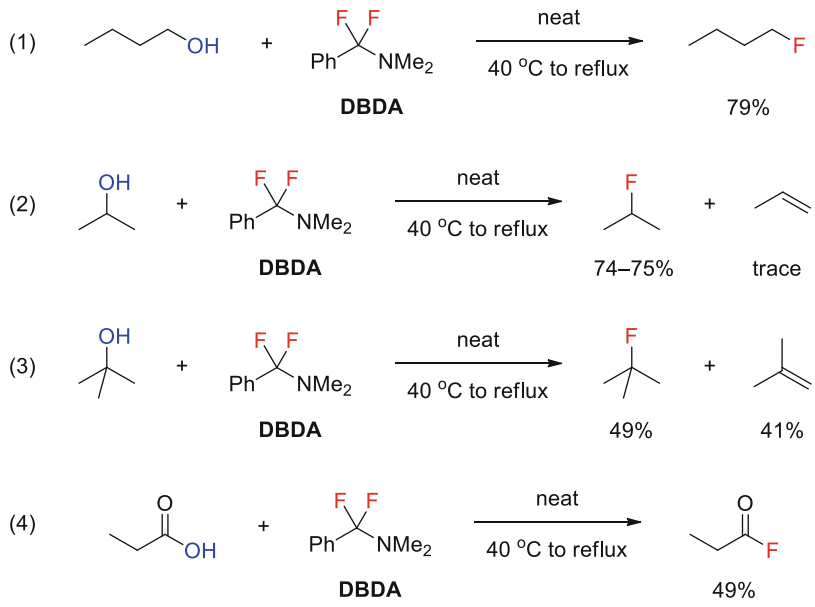
α,α-Difluorobenzylamines Deoxofluorination, Scheme 1 Preparation of DFMBA and its analogues

cleavage could be avoided and the substrate scope could be extended to *N,N*-dialkylbenzamides bearing various substitutes (Scheme 1, Eq. 2) [1, 5]. However, it is not safe and convenient to prepare DFMBA and its analogues with SF_4. One alternative method is to react *N,N*-dialkylbenzamides with oxalyl chloride followed by F-Cl exchange with Et_3N-3HF. DFMBA could be obtained in 82% yield by using the one-pot, two-step procedures (Scheme 1, Eq. 3) [3, 6]. Other DFMBA analogues could also be prepared similarly [7].

Deoxofluorination of Alcohols

In 1983, Dmowski and Kamiński reported the use of DBDA as a novel deoxofluorination reagent (Scheme 2) [1]. Primary, secondary, and tertiary alcohols as well as carboxylic acids with simple structures were converted to the corresponding organofluorides smoothly by DBDA under relatively mild conditions. Yields of the organofluorides are strongly dependent on the nature of the alcohols. For primary alcohols, high yields of the alkyl fluorides were obtained as the only product, whereas elimination products alkenes were generated as side products when secondary alcohols were subjected to the reaction. Commonly, the deoxofluorination of tertiary alcohols with fluoroalkylamine reagents (such as Ishikawa reagent $CHClFCF_2NEt_2$) rarely gave tertiary fluorides [8]; however, the reaction with α,α-difluorobenzylamines is an exception. For example, *tert*-butyl alcohol can react with DBDA to afford 49% yield of *tert*-butyl fluoride (Scheme 2, Eq. 3) [1]. Besides, propionyl fluoride was obtained when propionic acid was used to react with DBDA (Scheme 2, Eq. 4) [1].

DFMBA was initially reported for the deoxofluorination of sugars by Hara and co-workers. A primary hydroxy group in carbohydrates was converted to the corresponding fluoride in moderate to high yields at relatively high temperatures. Under microwave heating conditions, the reaction proceeded more quickly, and sometimes higher yield could be obtained (Scheme 3, Eqs. 1 and 2). The reaction can be conducted in various solvents, such as heptane, dodecane, and dioxane, and hydrocarbon solvent is superior to other solvents when microwave irradiation condition was used. Under proper reaction conditions, deoxofluorination with DFMBA could afford good chemoselectivity.



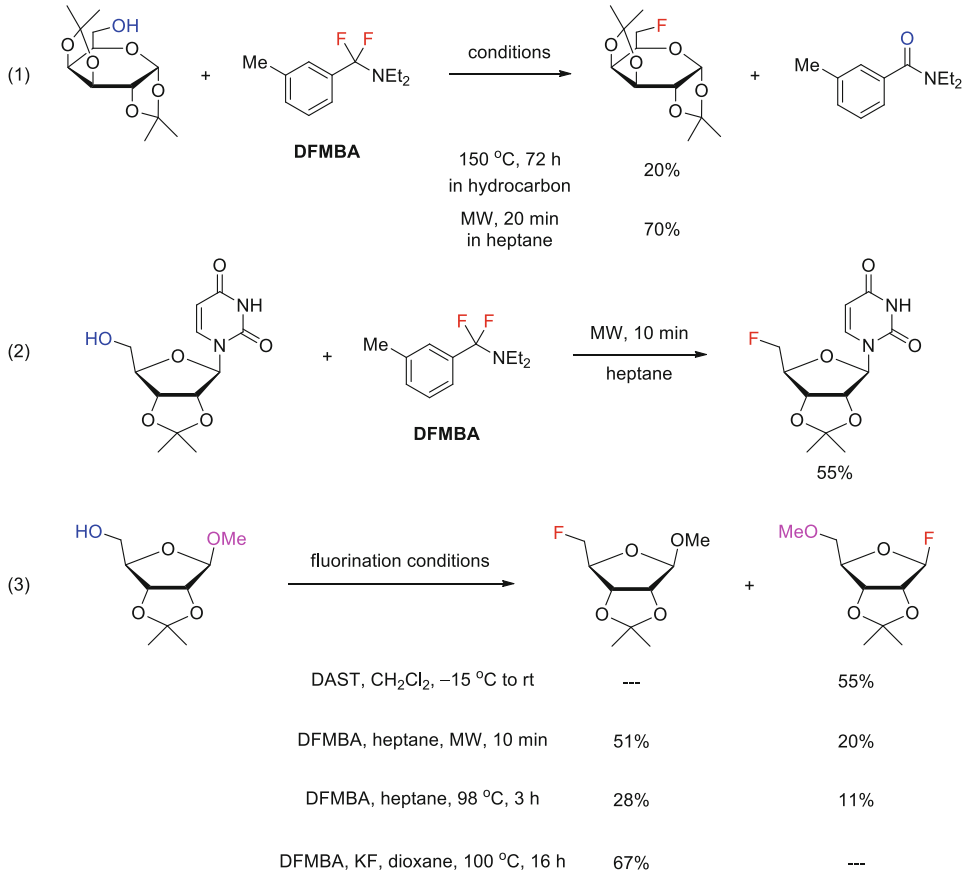
***α,α*-Difluorobenzylamines Deoxofluorination, Scheme 2** Deoxofluorination with α,α-difluorobenzyl(dimethyl) amine (DBDA)

For example, DAST was previously used to react with methyl 2,3-*O*-isopropylidene-*β*-D-ribofuranose; however, an unexpected 5-*O*-methyl-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl fluoride was obtained instead of the desired 5-deoxo-5-fluoro derivative product (Scheme 3, Eq. 3) [9]. This product was generated via the migration of the methoxy group from 1- to 5-position. When DFMBA was used as the deoxofluorination agent under microwave heating conditions, the corresponding fluorinated product was obtained in 51% yield, along with only 20% yield of the methoxy group migrated product. However, conducting the reaction under thermal conditions gave the fluorinated and the migration product in only 28% and 11% yields, respectively. Fortunately, the methoxy group migration can be avoided by carrying out the reaction in dioxane at 100 °C in the presence of KF, and the desired fluorination product could be obtained in up to 67% yield [2, 10].

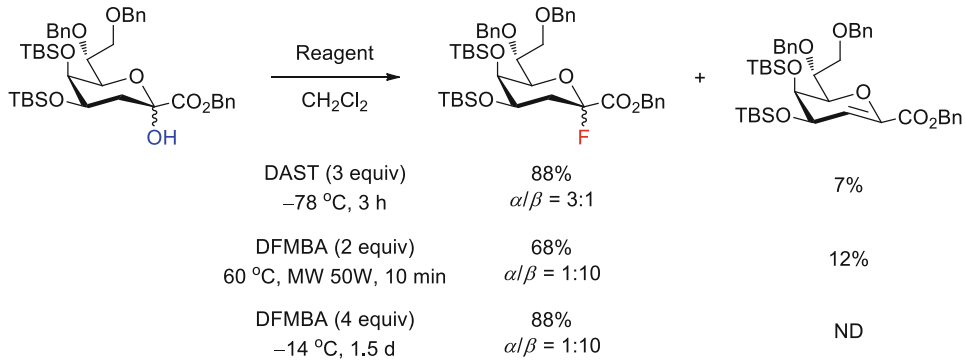
The hydroxy groups at the anomeric position of the sugars is highly reactive, thus even hydrogen fluoride pyridine can be used for the conversion of the sugars to glucosyl fluorides [11]. However, such conditions cannot tolerate some acid-sensitive protecting groups such as the silyl groups. The use of DFMBA as the deoxofluorination reagent can address this problem, and various glycosyl fluorides with different protecting groups were prepared in good yields from the corresponding sugars at temperatures below room temperature. It is noteworthy that, compared to DAST, the anomeric stereoselectivity for fluorination with DFMBA can be different. For example, fluorination of a 3-deoxy-D-manno-oct-2-ulosonic acid derivative with DAST gives fluoride with $\alpha/\beta = 3/1$, while $\alpha/\beta = 1/10$ was obtained when DFMBA was used for deoxofluorination. Moreover, the elimination side reaction was precluded when DFMBA was used at a lower temperature (Scheme 4) [12].

Deoxofluorination of Multiple Alcohols

Selective fluorination of multiple alcohols is usually difficult due to the further fluorination

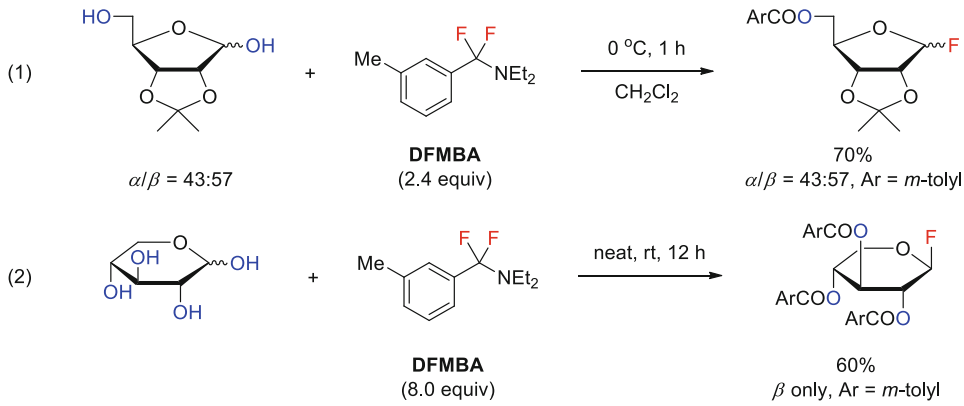


α,α-Difluorobenzylamines Deoxofluorination, Scheme 3 Deoxofluorination of primary hydroxy group in sugars with DFMBA



α,α-Difluorobenzylamines Deoxofluorination, Scheme 4 Deoxofluorination of anomeric hydroxy group in protected sugars

of the other hydroxyl group. The use of difluorobenzylamines can realize selective fluorination. Hara and co-workers reported that anomeric hydroxy groups in sugars can be selectively converted to fluoride using DFMBA, in this case, other hydroxy groups were in situ protected by *m*-methylbenzoyl group (Scheme 5) [2, 10].



α,α-Difluorobenzylamines Deoxofluorination, Scheme 5 Deoxofluorination of anomeric hydroxy group in unprotected sugars

Similarly, DFMBA can react with 1,2- and 1,3-diols to afford the corresponding monofluorinated products with one hydroxy group being in situ protected by *m*-methylbenzoyl group (Scheme 6, Eq. 1) [13]. The reaction can be performed under conventional thermal heating conditions with good yields; under microwave irradiation conditions, the reaction proceeds much faster. In the cases of optically active diols, monofluorination products are obtained with high diastereoselectivity [13, 14]. It is noteworthy that, hydroxy groups at the allylic position can be fluorinated exclusively (Scheme 6, Eq. 2) [14]. Mechanistically, the reaction is likely to proceed through a cyclic intermediate, which can undergo nucleophilic substitution by fluoride ion to afford the alkyl fluoride, accompanying the formation of a stable ester group (Scheme 6, Eq. 3) [13]. Based on this reaction mechanism, the reactions of 1,2- and 1,3-diols with *N, N*-diethyl-4-methoxybenzamide diethyl acetal in the presences of Et_3N-3HF as the fluoride source also afford the corresponding monofluorination products in moderate to good yield (Scheme 6, Eq. 4) [15]. In addition, amino alcohols can also be fluorinated via the same process, with the amino group being protected by benzoyl (Scheme 6, Eq. 5) [16]. Note that when the reaction of diols with α,α-difluorobenzylamines is conducted at low temperatures, the cyclic amide acetal intermediates are fluorinated slowly, thus quenching with H_2O can afford the monobenzoylation products (Scheme 6, Eq. 6) [17].

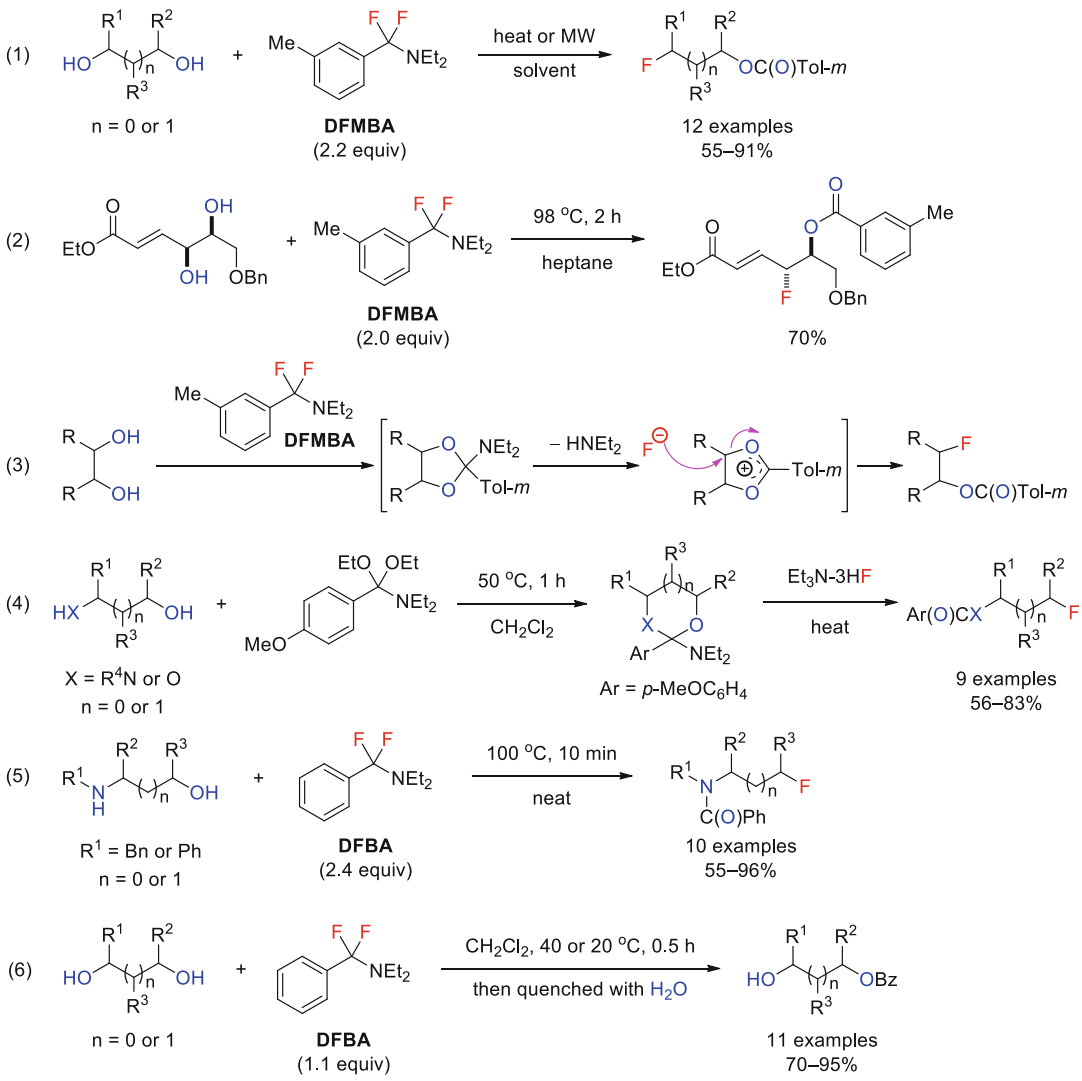
Deoxofluorination of Epoxides

Vicinal difluorides can be prepared via the ring-opening reaction of epoxides with amine-HF adducts followed by deoxofluorination of the so-obtained fluorohydrines with DAST [18, 19]. However, the overall yields of this two-step procedure were not high. Hara and co-workers showed that using DFMBA under microwave-irradiation conditions dramatically accelerate both the ring-opening of epoxides and the subsequent deoxofluorination [2, 10], thus treating epoxides with Et_3N-3HF and DFMBA in one pot under the irradiation of microwave could afford the corresponding difluoro compounds in good yields (Scheme 7) [20].

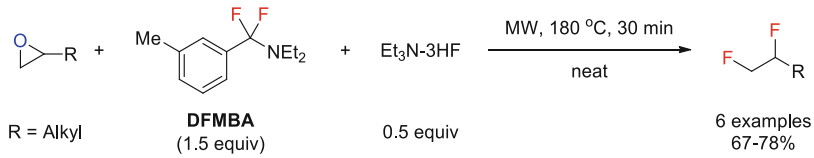
Deoxofluorination of Carbonyl Compounds

In the presence of Et_3N-3HF, DFMBA reacts with various aromatic and aliphatic aldehydes to afford the corresponding *gem*-difluorides in good yields (Scheme 8, Eq. 1) [6]; however, the reaction of DFMBA with ketone is sluggish. As a result, for those substrates containing both ketone and aldehyde groups, the aldehyde group could be selectively converted to the corresponding *gem*-difluoride (Scheme 8, Eq. 2) [6].

DMFBA can react with β-diketones at relatively lower temperatures to afford the

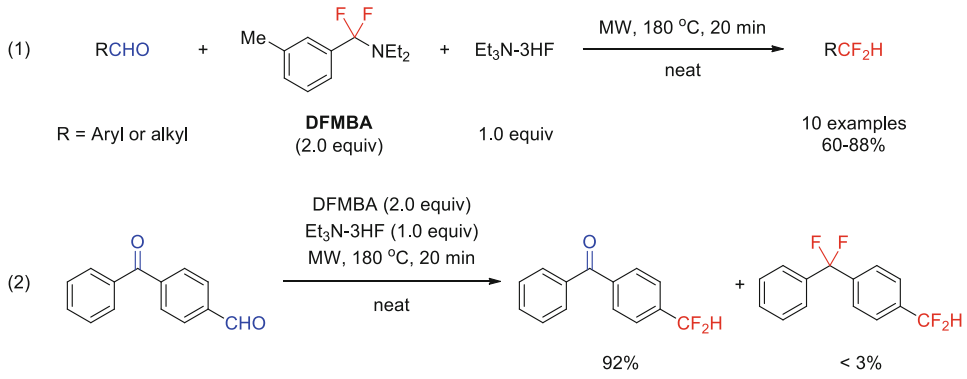


α,α-Difluorobenzylamines Deoxofluorination, Scheme 6 Deoxofluorination of diols and amino alcohols

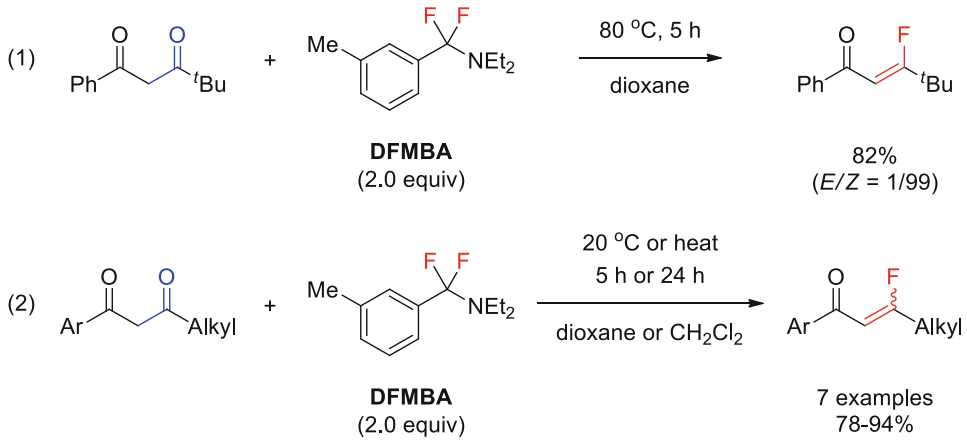


α,α-Difluorobenzylamines Deoxofluorination, Scheme 7 Deoxofluorination of epoxides

corresponding β-fluoro-α,β-unsaturated ketones in good yields (Scheme 9) [21]. Generally, a mixture of *E*- and *Z*-isomers are obtained; however, when the β-diketones are substituted with bulky groups, the products could be generated with high stereoselectivity (Scheme 9, Eq. 1). For unsymmetrical 1-aryl-1,3-diketones, only the carbonyl group attached to the alkyl group can be fluorinated (Scheme 9, Eq. 2).



α,α-Difluorobenzylamines Deoxofluorination, Scheme 8 Deoxofluorination of aldehydes



α,α-Difluorobenzylamines Deoxofluorination, Scheme 9 Deoxofluorination of β-diketones

Conclusion and Future Directions

In conclusion, difluorobenzylamine reagents show good thermal stability and deoxofluorination reactivity. Among various difluorobenzylamine reagents, DFMBA was well studied by Hara and co-workers. By using microwave irradiation or conventionally heating conditions, various alcohols, diols, epoxides, aldehydes, and β-diketones have been converted to the corresponding fluorides in good yields. Moreover, many sugar substrates can be deoxofluorinated by DFMBA to give better results than DAST. However, DFMBA is less efficient than DAST in the deoxofluorination of ketones.

Cross-References

- 2,2-Difluoro-1,3-Dimethylimidazolidine (DFI) Deoxofluorination
- CpFluor Deoxofluorination
- Fluoroolefin-Amine Adduct Deoxofluorination
- PhenoFluor Deoxofluorination
- Tetramethylfluoroformamidinium Hexafluorophosphate (TFFH) Deoxofluorination

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