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[Bis(2-methoxyethyl)amino]sulfur Trifluoride, the Deoxo-Fluor Reagent: Application toward One-Flask Transformations of Carboxylic Acids to Amides

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Abstract: The use of the Deoxo-Fluor reagent is a versatile method for acyl fluoride generation and subsequent one-flask amide coupling. It provides mild conditions and facile purification of the desired products in good to excellent yields. We have explored the utility of this reagent for the one-flask conversion of acids to amides and Weinreb amides and as a peptide-coupling reagent.

Acyl fluorides are versatile functional groups in organic chemistry due to the unique nature of the carbonyl−fluorine bond.[1] Many useful chemical transformations are elicited via this functionality since it possesses greater stability than the corresponding acid chloride toward neutral oxygen nucleophiles, yet is of high reactivity toward anionic nucleophiles and amines.[2] It has been observed that acid fluorides react more like activated esters than acid halides (Cl, Br, I).[2] For example, Fmoc,[3,4] Boc, and Cbz amino acid fluorides[5] were found to be stable, rapid-acting, acylating reagents for peptide bond formation. It is also of note that no significant loss of optical purity is observed during the conversion of acid fluorides to amides.[5,6] These properties make shelf-stable acid fluorides possible and allow for their isolation through organic extraction. It is these characteristics which make them important for further synthetic study.[1]

A variety of techniques are available for the generation of acyl fluorides.[1,2] There are, however, disadvantages associated with these methods, including poor yields, dangerous or toxic chemicals, forcing reaction conditions, and costly reagents. A recently developed alternative, [bis(2-methoxyethyl)amino]sulfur trifluoride,the Deoxo-Fluor reagent (**1**), which was first described by Lal et al. as a thermally stable alternative to the DAST reagent (**2**), overcomes several of these problems (Figure 1).[7,8] The initial investigation of this reagent showcased its utility for the conversion of hydroxy alkanes to the corresponding alkyl fluorides (deoxygenation−fluorination).[8] Additional transformations were explored as well, including the conversion of carboxylic acids to acyl fluorides.[7] Based on these observations, we sought to take advantage of the properties of acyl fluorides combined with this new and facile protocol for their preparation. Our efforts have led to a one-flask protocol for the conversion of carboxylic acids to a variety of amides obtained through an intermediate acyl fluoride. A full account of this work is presented herein.[9]

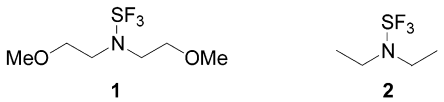

FIGURE 1. Structures of Deoxo-Fluro (**1**) and DAST (**2**).

Conversion of Carboxylic Acids to Amides. The importance of amides cannot be overstated as they are crucial in the architecture of biological systems and prevalent in natural products and commercial medicines, and their formation is widely utilized in the construction of many molecules/materials. A special group of amides which shows additional versatility are the *N*,*O*-dimethylhydroxylamides (Weinreb amides).[10] These compounds have become important and widely used building blocks in organic synthesis.[11−14] Accordingly, several methods are available for their formation including the direct conversion of carboxylic acids to amides. Some of these procedures utilize peptide coupling reagents such as BOP,[15,16] DCC,[17] or propylphosphonic anhydride/*N*-ethylmorpholine.[18,19] Einhorn et al. have developed a method for the synthesis of Weinreb amides from carboxylic acids using carbon tetrabromide and triphenylphosphine.[20] Sibi et al. have reported the synthesis of Weinreb amides from carboxylic acids using 2-chloro-1-methylpyridinium iodide (CMPI) or BMPI as the coupling agent.[21] Drawbacks of these methods include expensive coupling reagents and difficult removal of excess reagent and reagent byproducts. Therefore, a continued interest exists in the development of alternative methods for amide formation from carboxylic acids that are operationally simple and allow for easy removal of reagents and reagent byproducts.

In the course of our study, we found that carboxylic acids could be readily converted to the corresponding

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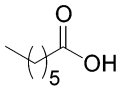
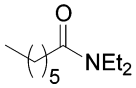
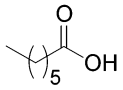
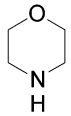
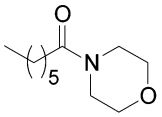
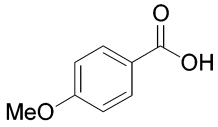
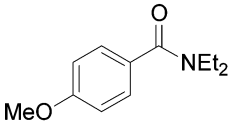
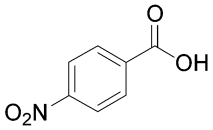
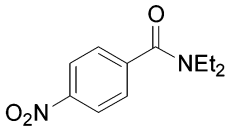
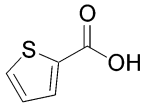
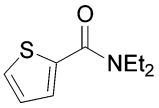
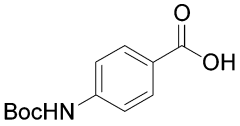
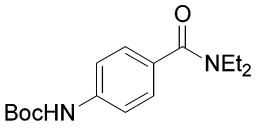
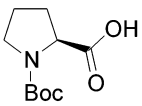
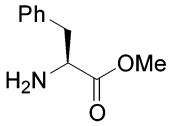
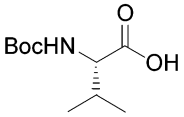
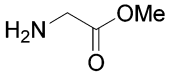
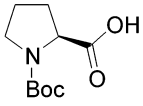
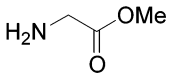
TABLE 1. Preparation of Amides[a]

Entry	Substrate	Amine	Product	Compound Number	Yield (%)[b]	Reaction Time (hr)
1		$HNEt_2$		**3**	98	2
2				**4**	74	5
3		$HNEt_2$		**5**	98	2
4		$HNEt_2$		**6**	96	3
5		$HNEt_2$		**7**	93	2
6		$HNEt_2$		**8**	67	2
7			Boc-Pro-Phe-OMe	**9**	75	8
8			Boc-Val-Gly-OMe	**10**	87	6
9			Boc-Pro-Gly-OMe	**11**	77	6

[a] All compounds in Table 1 were prepared via method A (see the Experimental Section, general procedures). [b] Isolated yield.

amides and peptides (Table 1) or Weinreb amides (Table 2) in a one-flask protocol by using the Deoxo-Fluor reagent. This procedure met our goals by providing a straightforward method where the resulting byproducts of the reaction[22] can be easily removed. As shown in Tables 1 and 2, a variety of amides can be prepared from commercially available carboxylic acids. Saturated aliphatic and cyclic acids were cleanly converted to the corresponding amides (entries 1 and 2, Table 1; entries 1 and 3, Table 2). We also prepared the Weinreb amide from *trans*-crotonic acid in good yield (entry 2, Table 2). Benzoic acids with electron-withdrawing and electron-releasing groups (entries 3 and 4, Table 1; entry 5, Table 2) and 2-thiophenecarboxylic acid (entry 5, Table 1; entry 6, Table 2) provided good yields of the amides. This methodology is also applicable to the synthesis of Weinreb amides from amino acids (entries 7−10, Table 2). Carpino has extensively studied and shown many of the advantages of utilizing amino acid fluorides in peptide bond formation.[3−5,23,24] As seen in Table 1 (entries 7−9), dipeptides can similarly be generated utilizing this reagent. The generation of these chiral Weinreb amides and peptides illustrates the amenability of this procedure for a racemization free protocol as determined by optical rotation and chiral HPLC.

Additional Observations. In our experimentation, an observation was made related to substrate compat-

(22) Reagent byproducts SO_2 (gas) and $HN(CH_2CH_2OMe)_2$ (liquid bp 170−176 °C) are easily removed under reduced pressure: *Chem. Ber.* **1959**, *92*, 1789−1797.

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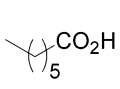
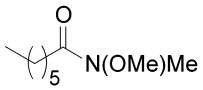
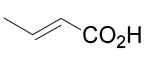
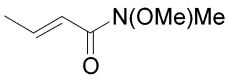
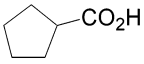
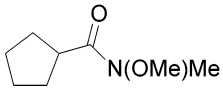
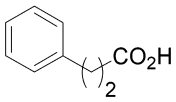
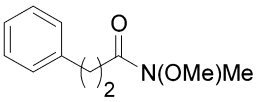
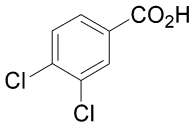
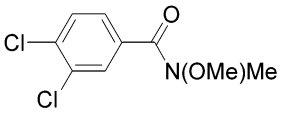
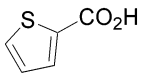
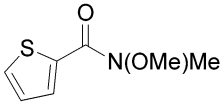
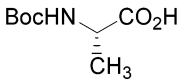
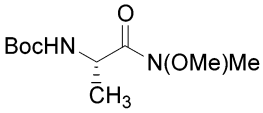
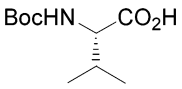
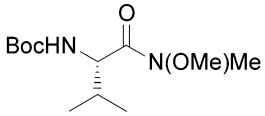
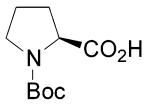
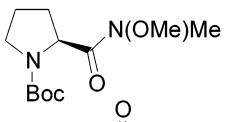
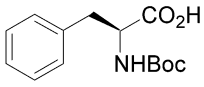
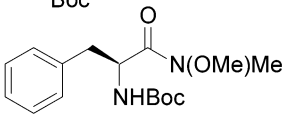
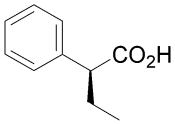
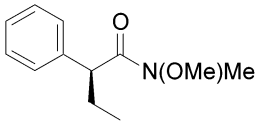
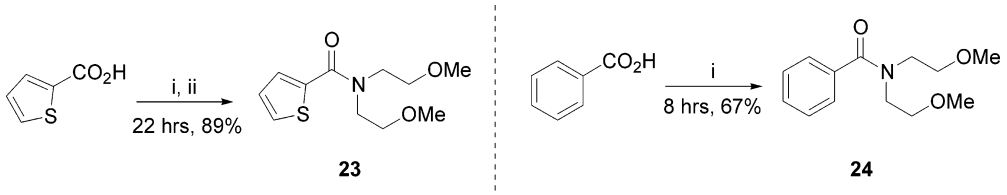
TABLE 2. Preparation of Weinreb Amides

Entry	Substrate	Product	Method[a]	Compound Number	Yield (%)[b]	Reaction Time (hr)
1			B	**12**	82	3
2			A	**13**	73	8
3			B	**14**	85	4
4			B	**15**	86	8
5			B	**16**	92	4
6			B	**17**	76	5
7			A	**18**	90	6
8			A	**19**	91	6
9			A	**20**	86	3
10			A	**21**	89	5
11			B	**22**	83	4

[a] All compounds in Table 2 were prepared via method A or B as indicated (see the Experimental Section, general procedures). [b] Isolated yield.

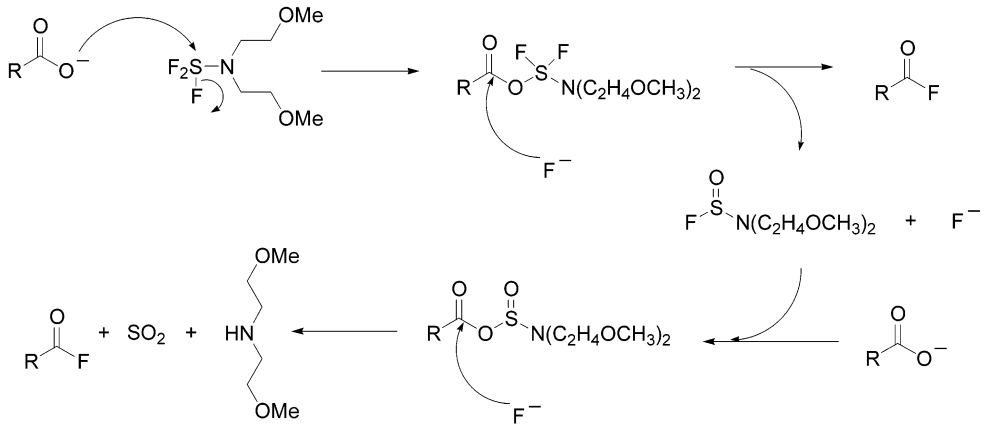
ibility in regards to this method. When we attempted to add *N*,*N*-diisopropylamine to the corresponding acyl fluoride of 2-thiophenecarboxylic acid, none of the desired diisopropylamide product was formed. Instead, we obtained the bis(methoxyethyl)amide exclusively (Scheme 1, **23**). In a proposed mechanism for acyl fluoride formation utilizing **1** (Scheme 2) the corresponding bis(methoxyethyl)amine is generated along with SO_2.[33] We propose that in the case of sterically encumbered amines, or a lack of external amine, the bis(methoxyethyl)amine side product is able to participate in the acylation reaction. This hypothesis was confirmed by treating benzoic acid with the Deoxo-Fluor reagent under our typical conditions for acid fluoride formation (Scheme 1). The reaction mixture was allowed to stir for a period of 8 h without the addition of an external, secondary amine. Upon completion, 67% of the corresponding bis(methoxyethyl)amide (Scheme 1, **24**) was generated. It has been demonstrated with this reagent[7] and DAST[4] that the intermediate acyl fluoride can be readily isolated. Typical

SCHEME 1



i) Deoxo-Fluor™, *N*,*N*-diisopropylethylamine, CH_2Cl_2; ii) *N*,*N*-diisopropylamine

SCHEME 2



reaction times in these cases are 10−30 min. The resultant product can then be treated with the desired nucleophile in a second step.[3−6] This two step protocol would remedy the side product formation, however, the advantage of the one-flask reaction sequence would be lost.

The use of the Deoxo-Fluor reagent was shown to be a versatile method for acyl fluoride generation and subsequent one-flask amide coupling. It provides mild conditions and facile purification of the desired products and proceeds in good to excellent yields. We have explored the utility of this reagent for the one-flask conversion of acids to amides, Weinreb amides, and as a peptide-coupling reagent. Overall, this method appears to be a robust and easily utilized technique for the aforementioned processes.

Experimental Section

General Procedure. Method A. The carboxylic acid (1 equiv) was dissolved in CH_2Cl_2 under an argon atmosphere, cooled to 0 °C, and then *N*,*N*-diisopropylethylamine (1.5 equiv) and [bis(2-methoxyethyl)amino]sulfur trifluoride (1.2 equiv) were added dropwise. After being stirred for 15−30 min (acyl fluoride formation), a solution of the amine (1.5 equiv) in CH_2Cl_2 was added. This mixture was stirred at 0 °C for an additional 15 min and then allowed to warm to room temperature. Stirring was continued for 3−8 h (monitored by TLC). After completion, the reaction was diluted with additional CH_2Cl_2 and sequentially extracted with aqueous saturated sodium bicarbonate, water, and brine. The organic layer was then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification via silica gel column chromatography then provided the final product.

Method B. In cases where the substrate was not soluble in CH_2Cl_2, *N*,*N*-dimethylformamide could be used. The same molar ratios were used; however, the workup protocol required dilution of the crude reaction mixture in ether, with sequential extraction using aqueous saturated sodium bicarbonate, water, and brine as before.

Enantiopurity Determination. The dipeptides, compounds **9**−**11**, were evaluated on the basis of reported optical rotations (see the Supporting Information for references). The enantiopurity of compounds **18**−**20** and **22** was determined by HPLC analysis. HPLC analysis was conducted using the Chiralcel AD-RH column: solvent, hexanes/2-propanol (95/5); flow rate, 1.00 mL/min; detection 225 nm. Retention times (in minutes) was found as follows: **18** (*R*) 8.2, **18** (*S*) 6.6; **19** (*R*) 7.9, **19** (*S*) 8.7; **20** (*R*) 7.0, **20** (*S*) 6.0; **22** (*R*) 5.6, **22** (*S*) 6.4. Compound **21** could not be resolved under these conditions. The optical purity was >97% for all compounds.

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Supporting Information Available: A description of general methods and characterization data for all new compounds (**3**, **4**, **8**, **14**, **16**, **17**, **23**, and **24**). Compounds **5**,[25] **6**,[26] **7**,[27] **9**,[5] **11**,[28] **12**,[29] **13**,[20] **15**,[30] and **18**−**22**[11,20,31,32] have been previously reported. Our spectroscopic data were in agreement with the reported values. Compound **10** is commercially available. This material is available free of charge via the Internet at http://pubs.acs.org.

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