ORGANIC LETTERS

2000
Vol. 2, No. 25
4091−4093

A One-Flask Synthesis of Weinreb Amides from Chiral and Achiral Carboxylic Acids Using the Deoxo-Fluor Fluorinating Reagent

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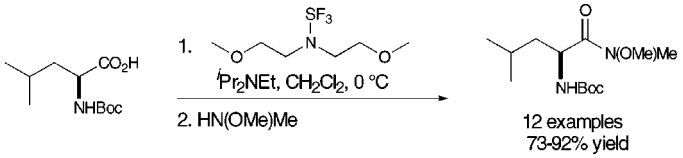
Received October 18, 2000

ABSTRACT



The reagent [bis(2-methoxyethyl)amino]sulfur trifluoride (Deoxo-Fluor reagent) converts carboxylic acids to the corresponding acid fluorides, which then react with *N*,*N*-dimethylhydroxylamine to give the corresponding Weinreb amides in high yields. The reaction proceeds without racemization when optically active acids are used as the starting material. This method is operationally simple and provides the products in high purity.

N-Methoxy-*N*-methyl amides (Weinreb amides)[1] have become important and widely used building blocks in organic synthesis.[2a−c,3a] Several methods are available for the direct conversion of carboxylic acids to the corresponding Weinreb amides.[2a,3] Some of these procedures utilize peptide coupling reagents such as BOP,[4,5] DCC,[6] or propylphosphonic anhydride/*N*-ethylmorpholine.[7,8] Einhorn et al. have developed a method for the synthesis of Weinreb amides from carboxylic acids using carbon tetrabromide and triphenylphosphine.[9] Recently Sibi et al. reported the synthesis of Weinreb amides from carboxylic acids using 2-chloro-1-methylpyridinium iodide (CMPI) or BMPI as the coupling agent.[10] Drawbacks of some of these methods are that some coupling reagents are expensive and that removal of excess reagent and reagent byproducts from the reaction product can be difficult. Therefore, a continued interest exists in the development of methods for Weinreb amide formation from carboxylic acids that are operationally simple and allow easy removal of reagents and reagent byproducts.

We are now detailing a novel, convenient, high yielding (73−92%), one-flask synthesis of Weinreb amides from chiral and achiral carboxylic acids using the Deoxo-Fluor reagent ([bis(2-methoxyethyl)amino]sulfur trifluoride).[11,12] In

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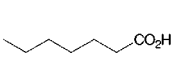
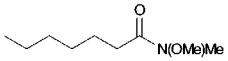
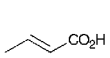
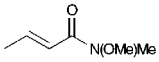
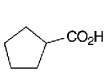
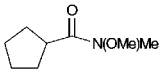
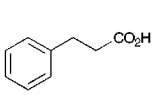
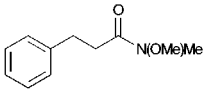
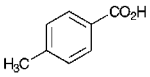
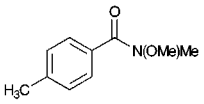
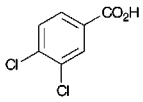
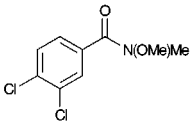
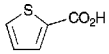
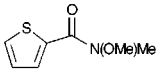
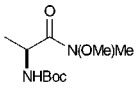
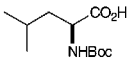
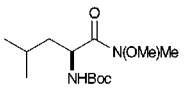
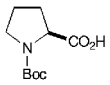
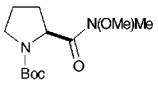
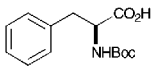
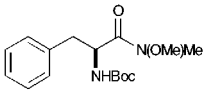
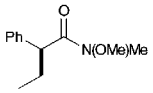
10.1021/ol000318w CCC: $19.00
Published on Web 11/14/2000

Table 1. Synthesis of Weinreb Amides from Carboxylic Acids[20]

entry	acid	product	method	yield (%)	reaction time (hr)
1			B	82	3
2[9]			A	73	8
3			B	85	4
4			B	86	8
5			B	91	4
6			B	92	4
7			B	76	5
8[10,20]			A	90	6
9[3b,20]			A	91	6
10[10,20]			A	86	3
11[3c]			A	89	5
12[9]			B	83	4

this procedure, carboxylic acids are first converted into acid fluorides by the Deoxo-Fluor reagent in the presence of *N*,*N*-diisopropylethylamine. Weinreb amides are formed after addition of *N*,*O*-dimethylhydroxylamine to the intermediate acid fluorides (Scheme 1 and Table 1).

Acyl fluorides possess stability greater than that of the corresponding acid chlorides toward neutral oxygen nucleophiles such as water and methanol yet are of high reactivity toward anionic nucleophiles and amines.[13] It has been observed that acid fluorides react more like active esters than acid halides (Cl, Br, I).[13] For example, α-Fmoc,[14] Boc, or Z amino acid fluorides[15] 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.[14,16] We are now reporting that the Deoxo-Fluor reagent is a versatile, easy to use reagent for the preparation of acid fluorides, which can be converted to the corresponding Weinreb amides

(11) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M. *Chem. Commun*. **1999**, 215−216.
(12) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem*. **1999**, *64*, 7048.
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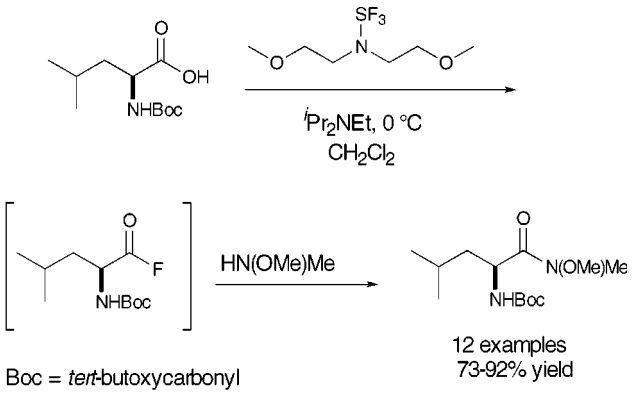
(16) Bertho, J.-N.; Loffet, A.; Pinel, C.; Reuther, F.; Sennyey, G. *Tetrahedron Lett*. **1991**, *32*, 1303.

Scheme 1



in a one-flask procedure. To the best of our knowledge, no reports have yet appeared on the conversion of acid fluorides into Weinreb amides. The combination of effective fluorination properties, enhanced safety features compared to DAST, and commercial availability will make this reagent a cost-effective alternative for many uses.[11,12]

In a typical experiment (method A) the carboxylic acid (1 equiv) was dissolved in CH_2Cl_2 under an argon atmosphere, cooled to 0 °C, and then treated with diisopropylethylamine (1.5 equiv) and [bis(2-methoxyethyl)amino]sulfur trifluoride (1.2 equiv). After stirring for 15 min (acid fluoride formation), a solution of *N*,*O*-dimethylhydroxylamine (1.5 equiv) in CH_2Cl_2 was added.[17] 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) at ambient temperature. After completion, the reaction was diluted with additional CH_2Cl_2 and was then extracted sequentially with aqueous $NaHCO_3$, aqueous NH_4Cl solution, and brine. The organic layer was then dried over magnesium sulfate and concentrated under reduced pressure.

In cases where the substrate was insoluble in CH_2Cl_2, we used DMF as the solvent (Method B). The same molar ratios were used as in method A. The preparation of the *N*,*O*-dimethylhyroxylamine was also carried out as previously described, but with DMF as the solvent.[17] Upon completion, the reaction mixture was taken up in ether and sequentially extracted with water, aqueous $NaHCO_3$, aqueous NH_4Cl, and brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure.

The crude products were purified by short path silica gel column chromatography. The yields in Table 1 refer to isolated yields, obtained after purification.[18]

As shown in Table 1, a variety of *N*-methoxy-*N*-methyl amides were prepared from commercially available carboxylic acids. Saturated aliphatic and cyclic acids were cleanly converted to the corresponding Weinreb amides (entries 1, 3, 4, and 12). We also prepared the Weinreb amide from *trans*-crotonic acid in good yield (entry 2). Benzoic acids with electron-withdrawing and electron-releasing groups (entries 5 and 6) and 2-thiophenecarboxylic acid (entry 7) provided good yields of the Weinreb amides. This methodology is also applicable to the synthesis of Weinreb amides of amino acids (entries 8−11). It is of further interst to note that no racemization was seen at the chiral center of these amino acids as determined by HPLC.[18]

In conclusion, we have developed a new and operationally simple method for the synthesis of *N*-methoxy-*N*-methyl amides from carboxylic acids and *N*,*O*-dimethylhydroxylamine, using [bis(2-methoxyethyl)amino]sulfur trifluoride to activate the acids toward amide formation. This method is superior to some of the existing methods because excess reagent and reagent byproduct impurities are easily removable.[19] The use of [bis(2-methoxyethyl)amino]sulfur trifluoride for the formation of acid fluorides should also be of advantage for amide synthesis in the preparation of solid- and solution-phase combinatorial libraries.

Acknowledgment. We gratefully acknowledge financial support from the National Institutes of Health (NCI) and a NIH Predoctoral Training Grant (GM-08545 for J.M.W.). We also thank Air Products for providing the Deoxo-Fluor reagent as a gift.

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(17) Preparation of *N*,*O*-dimethylhydroxylamine solution in CH_2Cl_2. To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride in methylene chloride at 0 °C (ice−water bath) was added dropwise *N*,*N*-diisopropylethylamine (1.5 equiv). A clear, colorless solution was obtained after 5 min. This solution was kept cold until use in the reaction.[3b]

(18) All Weinreb amides in the table were characterized by ^1H NMR, ^{13}C NMR, MS, and optical rotation (where appropriate). The spectroscopic data were in agreement with the structures of the products. Compounds 2 and 8−12 are known compounds (see Table 1 for references). Optical rotations for Weinreb amides **8**−**12**: entry 8, found $[\alpha]_D$ −28 (c = 1.0, MeOH), lit. $[\alpha]_D$ −26 (c = 1.0, MeOH);[20] entry 9, found $[\alpha]_D$ −24 (c = 1.0, MeOH), lit. $[\alpha]_D$ −25.5 (c = 1.00, MeOH);[20] entry 10, found $[\alpha]_D$ −42 (c = 1.0, MeOH), lit. $[\alpha]_D$ −38 (c = 1.0, MeOH);[20] entry 11, found $[\alpha]_D$ +4.3 (c = 1.0, MeOH); entry 12, found $[\alpha]_D$ +57 (c = 1.0, MeOH). Further examination of entries 8−12 by HPLC showed that no racemization of the chiral center had occurred. Both the *R* and *S* enantiomers were prepared for comparison. HPLC analysis using the Chiralcel AD-RH column: solvent, hexanes/2-propanol (95/5); flow rate, 1.00 mL/min; detection 225 nm. Retention times (min): entry 8, (*R*) 8.2, (*S*) 6.6; entry 9, (*R*) 7.9, (*S*) 8.7; entry 10, (*R*) 7.0, (*S*) 6.0; entry 12, (*R*) 5.6, (*S*) 6.4. Entry 11 could not be resolved under these conditions. Optical purity was >97% for all compounds.

(19) Reagent byproducts SO_2 (gas) and $HN(CH_2CH_2OMe)_2$ (liquid, bp 170−176 °C) are easily removed under reduced pressure.

(20) The Weinreb amides in entries 8−10 are commercially available from Aldrich.