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Synthesis of 1,2,4-oxadiazole-linked orthogonally urethane-protected dipeptide mimetics

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ABSTRACT

The synthesis of a new class of 1,2,4-oxadiazole-linked orthogonally urethane-protected dipeptide mimetics is described. The protocol employs a reaction between an N-protected amino acyl fluoride and an amino acid-derived amidoxime. All the three commonly employed urethanes have been used in this protocol for N-protection. The course of the reaction was found to be high yielding and all new compounds were well characterized by NMR and mass spectroscopy. The *O*-acyl amidoxime intermediate has also been isolated as a stable solid.

1. Introduction

Peptidomimetics[1] are being explored largely to circumvent some of the disadvantages of native peptides and to increase the bioavailability and potency of peptide-based drugs.[2] Several types of non-natural linkages such as retro-amides, ureas,[3] carbamates,[4] sulfonamides,[5] thiazoles and[6] triazoles,[7,8] are used as amide bond replacements to obtain new classes of peptidomimetics with considerable success. 1,2,4-Oxadiazoles[9] are important amongst biologically active heterocycles, the utility of which has been extended to many potent classes of drug-related molecules such as ligands of benzodiazepine receptors,[10] muscuranic receptor agonists,[11] antiviral compounds, angiotensin II receptor antagonists[12] and HIV-1 reverse transcriptase inhibitors.[13] In peptide chemistry, this group has been studied mainly as an efficient amide and ester bond bioisoester.[14,15]

The development of a reliable method for the insertion of 1,2,4-oxadiazole into peptides finds utility in the synthesis of large libraries of small peptide segments for their biological and therapeutical scrutiny. The general synthesis of 1,2,4-oxadiazoles involves coupling of an amidoxime with an activated carboxyl group, yielding an *O*-acyl amidoxime followed by its dehydrative cyclization.[16] The cyclization of *O*-acyl amidoximes has been carried out employing exhaustive reflux conditions in DMF or pyridine with or without additives such as 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC), dicyclohexylcarbodiimide (DCC), 1,1′-carbonyldiimidazole (CDI), *O*-(benzotriazol-1-yl) *N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) and the Burgess reagent.[17] The use of a strong base such as NaOEt or tetrabutylammonium fluoride (TBAF) allows completion of the reaction even at rt.[18] 1,2,4-Oxadiazoles have been incorporated in the synthesis of a Phe-Gly segment mimetic in the biologically active peptides such as dermorphin, and in substance P.[19] A new variety of 1,2,4-oxadiazole-linked peptidomimetics have been reported via reaction of Boc-amino acid-derived amidoximes with succinic/glutaric acid anhydrides in DMF at reflux.[15] Similar chemistry was explored also for the synthesis of 1,2,4-oxadiazole-containing β^3-amino acids.[20] In one report, a solid-phase methodology was employed wherein Fmoc/Boc amino acid anhydrides were reacted with resin-bound amidoximes followed by cyclization.[21] The Buchanan group described a reaction between a Boc amino acid succinimidyl ester and simple amidoximes with the aid of EDC·HOBt followed by cyclization in refluxing pyridine to obtain the corresponding 1,2,4-oxadiazole.[22] To the best of our knowledge, the synthesis of 1,2,4-oxadiazole-linked orthogonally protected dipeptide mimetics, which serve as building blocks for preparation of the corresponding oligopeptide mimetics, is yet to be reported. In the present work, the synthesis of 1,2,4-oxadiazole-linked N,N′-orthogonally protected dipeptide mimetics by coupling of an N-protected amino acid-derived amidoxime with another orthogonally protected amino acid fluoride followed by cyclization is described.

The essential intermediate in the preparation of the 1,2,4-oxadiazole is an amidoxime, which in the present study was prepared from the corresponding amino acid-derived nitrile. Initially, Boc-protected alanyl nitrile, obtained by the dehydration

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of Boc-Ala-NH_2 using trifluoroacetic anhydride (TFAA)/TEA, was refluxed in ethanol along with hydroxylammonium chloride ($NH_2OH{\cdot}HCl$) and solid K_2CO_3 for 2 h (Scheme 1). The insoluble inorganics were filtered off, and the filtrate was concentrated to obtain amidoxime **1** as a stable solid. The generality of this reaction was demonstrated by the synthesis of a series of amidoximes. Organic bases such as triethyl amine (TEA) and pyridine were avoided in order to circumvent racemization. The use of powdered K_2CO_3 facilitated simpler isolation of the product in good yield and purity. This procedure was applied to several other Boc/Z-amino acid nitriles, and the corresponding amidoximes were isolated in satisfactory yields. However, use of the Fmoc group for amine protection resulted in a lower yield of the amidoxime due to its deprotection under the basic reaction conditions. The use of bases including TEA, pyridine, NaOEt and TBAF did not result in any improvement of the product yield.

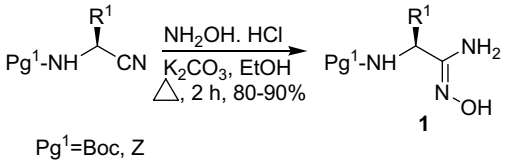
The *N*-urethane-protected amino acid fluorides[23,24] are well known as stable and useful acylating agents for racemization-free peptide coupling reactions. Unlike their acid chloride counterparts, acid fluorides are accessible to all three types of protecting groups, such as Fmoc, Z and Boc. Also, amongst various fluorinating reagents, Deoxo-Fluor[25,26] is gaining considerable interest for its fast and efficient reactivity in the preparation of acid fluorides. Upon treatment of an N-protected amino acid with Deoxo-Fluor in the presence of *N*-methylmorpholine (NMM) for 30 min, the corresponding acyl fluoride was isolated after a simple workup and recrystallization/precipitation. All the N-protected amino acyl fluorides prepared in this fashion were isolated as stable compounds.

For assembly of the title molecules, the N-protected amino acyl fluoride **2** was coupled to amino acid-derived amidoxime **1**. In a typical experiment, Boc-Gly-F was stirred with the amidoxime derived from Z-Ile-OH in the presence of NMM in ethanol. After 15 min, an equimolar quantity of sodium acetate was added and the reaction mixture was refluxed for 3 h. The resulting 1,2,4-oxadiazolyl dipeptide **3** was isolated after a simple workup followed by column chromatography as a pure solid in a yield exceeding 60% (Scheme 2). Several examples of 1,2,4-oxadiazole-containing dipeptide mimetics possessing different urethanes at the amino terminal were prepared, and consistently yields and purities were observed in all cases (Table 1).

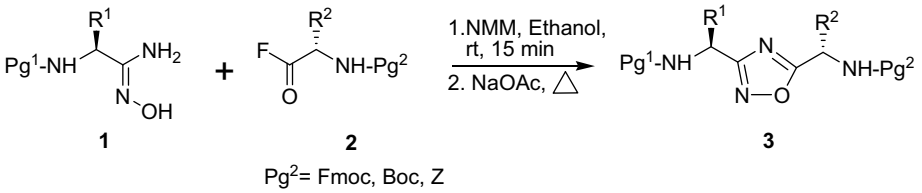
When the reaction was repeated without sodium acetate, the product 1,2,4-oxadiazole was isolated in low yield (<20%) even after refluxing for more than 6 h. The structures of all the synthesized 1,2,4-oxadiazolyl dipeptide mimetics **3** were confirmed through NMR and mass spectroscopy. Also the course of the reaction was proved to be racemization-free as was evident by HPLC analysis.

The protocol was extended by employing peptidyl counterparts of acyl fluoride and amidoxime units to prepare several 1,2,4-oxadiazole-linked tetrapeptides. The peptidyl amidoximes were prepared starting from the N-protected peptide acids in the same manner as described for **1**. They were isolated as stable solids in good yields, which were found to be enantiomerically pure as analyzed by HPLC. In a typical example, Z-Val-Gly-OH derived amidoxime **4a** was reacted with Fmoc-Ala-Phe-F **5a** (prepared by treating the peptide acid with Deoxo-Fluor) in the presence of sodium acetate in refluxing ethanol to afford the corresponding 1,2,4-oxadiazolyl tetrapeptide **6a** after 4 h. The material was isolated after a simple workup and column chromatography as a gum, which solidified slowly (Scheme 3).

The oxadiazole formation is a two-step process involving the formation of *O*-acyl amidoxime intermediate **7** followed by its cyclization. Consequently, we turned our interest to the isolation and characterization of **7**. Initially, Z-Val-F was added to a solution of Boc-Leu-OH derived amidoxime in ethanol followed by NMM at rt. After complete consumption of the acid fluoride (TLC), the reaction mixture was evaporated without heating and the residue was washed with water and hexane to afford the *O*-acyl amidoxime **7** as a stable solid (Scheme 4). Similarly, the reaction was repeated with a few other combinations of Fmoc/Boc/Z-amino acids and all the corresponding dipeptidyl *O*-acyl amidoximes **7** were obtained in satisfactory yields and purities (Table 2). Notably, the isolated *O*-acyl amidoxime, when subjected to cyclization in the presence of sodium acetate, gave slightly higher yields (>80%) of



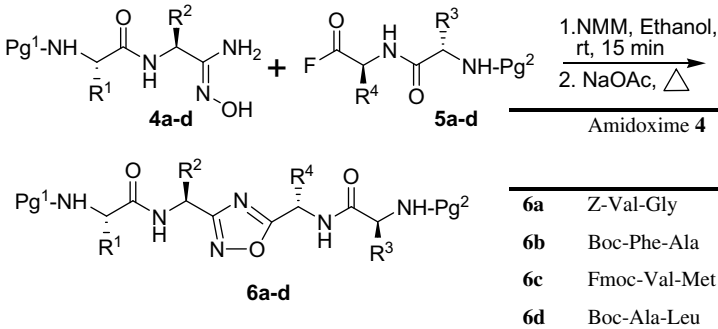
Scheme 1.



Scheme 2.

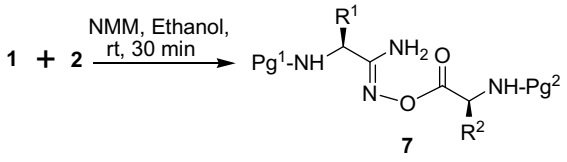
Table 1
1,2,4-Oxadiazole-linked dipeptide mimetics

Compd.	Pg^1	R^1	Pg^2	R^2	Yield (%)	Mp (°C)	$[\alpha]_D^{25}$ (*c* 1, DMF)
3a	Boc	$CH_2CH(CH_3)_2$	Z	$CH(CH_3)_2$	65	102	−27.14
3b	Boc	$CH_2C_6H_5$	Fmoc	$CH_2C_6H_5$	70	112	−31.36
3c	Boc	H	Z	$CH(CH_3)CH_2CH_3$	76	98	−26.80
3d	Boc	CH_3	Fmoc	$CH_2OCH_2C_6H_5$	68	114	−21.84
3e	Z	$CH(CH_3)CH_2CH_3$	Boc	H	71	101	−27.65
3f	Z	$CH_2CH(CH_3)_2$	Fmoc	$CH_2C_6H_5$	73	116	−36.26
3g	Z	$CH_2C_6H_5$	Boc	$CH_2COOCH_2C_6H_5$	68	104	−39.80
3h	Z	$CH_2C_6H_5$	Fmoc	C_6H_5	72	118	−24.10
3i	Fmoc	$CH_2CH(CH_3)_2$	Boc	CH_3	60	109	−27.31



	Amidoxime **4**	Acyl fluoride **5**	Yield (%)
6a	Z-Val-Gly	Fmoc-Ala-Phe	57
6b	Boc-Phe-Ala	Z-Leu-Gly	73
6c	Fmoc-Val-Met	Boc-Ala-Ile	52
6d	Boc-Ala-Leu	Z-Phe-Gly	71

Scheme 3.



Scheme 4.

Table 2
List of *O*-acyl amidoxime intermediates

Product	Amidoxime		Acyl fluoride		Yield (%)	$[\alpha]_D^{25}$ (*c* 1, DMF)
	Pg^1	Amino acid	Pg^2	Amino acid		
7a	Boc	Leu	Z	Val	72	−17.88
7b	Z	Ile	Boc	Gly	76	−18.56
7c	Z	Ala	Fmoc	Phe	73	−14.26
7d	Boc	Phe	Fmoc	Phe	79	−13.50
7e	Z	Gly	Boc	Asp(OBz)	70	−12.74

1,2,4-oxadiazoles **3** than those prepared without isolation of the intermediate (Scheme 5).

Finally, the orthogonality of the urethanes employed to protect the amino groups in the title compounds **3** was utilized for selective deprotection and peptide chain extension on either side. In a case study, **3a** was treated with trifluoroacetic acid (TFA) in CH_2Cl_2 to remove the Boc group. The free amino oxadiazole was reacted with Boc-Phe-F in the presence of TEA and the resulting peptide was isolated after a simple workup. Similarly, the procedure was repeated to couple Boc-Val-F to obtain another tripeptidomimetic molecule. Finally, 1,2,4-oxadiazole **3a** was subjected to catalytic hydrogenation using Pd-C/H_2 to deprotect the Z group. The resulting free amine was utilized for chain extension by coupling with Z-Ile-F or Z-Gly-F in presence of TEA. All the peptides were isolated in good yields (>70%).

In summary, we have developed a simple preparation of 1,2,4-oxadiazole-linked N,N′-orthogonally protected dipeptidomimetics by coupling the N-protected amino acid with another N-protected amino acid-derived amidoxime utilizing an acid fluoride group as the coupling agent. The resulting dipeptidomimetic building blocks were utilized for the preparation of 1,2,4-oxadiazole-linked oligopeptides through chain extension on either N-terminal.

2. General procedure for N-protected amino acid-derived amidoxime 1

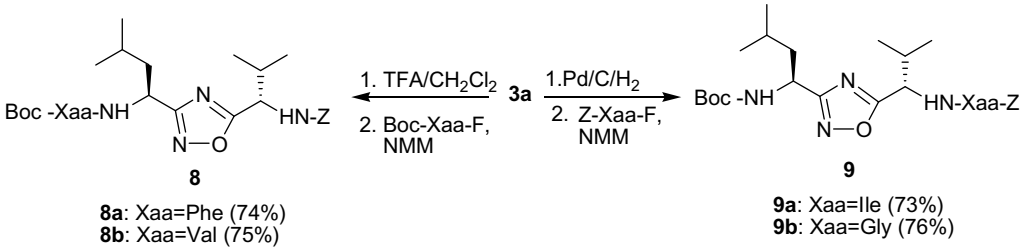
To a solution of N-protected amino acid nitrile (10 mmol) in ethanol were added $NH_2OH{\cdot}HCl$ (13 mmol) and powdered K_2CO_3 (13 mmol), and the reaction mixture was refluxed for 2 h. After the reaction was complete (TLC), the reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was triturated with hexane and the resulting solid was dried.

3. General procedure for the synthesis of 1,2,4-oxadiazolyl dipeptides 3

To a stirred solution of amidoxime **1** (2 mmol) in ethanol was added N-protected amino acyl fluoride (3 mmol) followed by NMM (5 mmol) at rt. After 10 min, NaOAc (2 mmol) was added and the reaction mixture was refluxed for 3 h. After completion of the reaction (TLC), ethanol was evaporated and the residue was suspended between ethyl acetate (15 mL) and water (10 mL). The organic layer was washed with 10% sodium carbonate solution (10 mL), water (15 mL × 2) and brine (15 mL). The organic layer was concentrated and the resulting crude compound was purified by column chromatography (silica gel 100–200 mesh, 20% ethyl acetate in hexane).

4. Spectral data for selected compounds

Compound **3a**: Solid; ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (m, 12 H), 1.32 (s, 9H), 1.65 (m, 3H), 2.45 (m, 1H), 4.53 (m, 2H), 5.41 (s,



Scheme 5.

2H), 6.35 (m, 2H), 6.9 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8, 21.9, 24.1, 31.2, 34.3, 51.3, 63.2, 69.3, 82.5, 127.1, 128.4, 128.8, 142.1, 155.3, 155.9, 156.6, 171.2, 175.5; HRMS calcd for $C_{24}H_{36}N_4NaO_5$: 483.2583, found 483.2579 [M+Na]; IR: 1701, 1697, 1657, 1634 cm^{-1}.

Compound **3c**: White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (m, 6H), 1.31 (s, 9H), 1.63 (m, 2H), 2.1 (m, 1H), 4.18 (s, 2H), 4.3 (m, 3H), 5.2 (m, 2H), 7.1–7.68 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 18.1, 23.1, 24.3, 31.1, 32.1, 45.8, 56.7, 62.8, 127.1, 127.9, 128.1, 128.6, 129.2, 156, 165.2, 170.1. HRMS calcd for $C_{21}H_{30}N_4O_5$: 441.2114, found: 441.2117 [M+Na]; IR: 1702, 1696, 1649, 1630 cm^{-1}.

Compound **3f**: Off white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, J = 6.4 Hz, 6H), 1.24 (t, J = 9.8, 3H), 1.65 (d, J = 6.8 Hz, 2H), 3.12 (m, 2H), 4.12 (d, J = 7.6 Hz, 2H), 4.23 (m, 3H), 5.1 (s, 1H), 5.32 (s, 1H), 6.9–7.7 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 22.6, 25.1, 38.7, 43.7, 46.8, 50.2, 55.2, 62.0, 67.6, 120.5, 125.5, 127.5, 127.9, 128.2, 128.7, 129, 129.2, 129.7, 129.8, 135.0, 136.2, 141.8, 144.2, 156.0, 171.3, 172.0, 172.6; HRMS calcd for $C_{38}H_{38}N_4NaO_5$: 653.274, found: 653.2781 [M+Na]; IR: 1712, 1696, 1652, 1640 cm^{-1}.

Compound **6a**: Off white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, J = 6.6 Hz, 3H), 1.37 (d, J = 6.8 Hz, 6H), 1.81 (m, 3H), 3.9 (m, 3H), 4.2–4.43 (m, 5H), 4.52 (m, 2H), 5.32 (m, 2H), 6.1 (br, 4H), 7.2–8.1 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8, 17.0, 31.5, 36.8, 45.1, 48.1, 50.3, 56.1, 63.4, 65.1, 68.7, 125.0, 126.8, 127.7, 127.9, 128.0, 128.2, 128.3, 128.7, 128.9, 129.6, 138.4, 141.0, 142.2, 144.6, 156.5, 156.9, 163.4, 172.4, 173.0, 176.1; HRMS calcd for $C_{42}H_{46}N_6NaO_8$: 785.3275, found: 785.3281 [M+Na]; IR: 1708, 1698, 1666, 1634 cm^{-1}.

Compound **6b:** White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, J = 6.8 Hz, 6H), 1.02 (d, J = 5.8 Hz, 3H), 1.2 (m, 2H), 1.34 (s, 9H), 2.31 (m, 3H), 4.25 (s, 2H), 4.4–4.53 (m, 5H), 5.2 (br, 2H), 5.5 (m, 2H), 7.1–7.9 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.9, 18.3, 22.9, 27.0, 36.0, 39.3, 42.1, 53.0, 56.0, 61.1, 65.3, 68.6, 121.1, 124.2, 125.3, 125.8, 129.3, 129.9, 131.1, 132.3, 134.5, 149.0, 151.2, 156.0, 160.0, 169.0, 172.5; HRMS calcd for $C_{33}H_{44}N_6NaO_7$: 659.3169, found: 659.3172 [M+Na]; IR: 1712, 1696, 1652, 1640 cm^{-1}.

Compound **7a**: Solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93–0.96 (m, 12H), 1.41 (s, 9H), 1.68 (m, 2H), 2.31 (m, 2H), 3.7 (t, J = 8.1 Hz, 2H), 4.13 (m, 2H), 5.54 (m, 2H), 5.87 (br, 2H), 7.2–7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 19.6, 22.5, 23.1, 29.0, 33.2, 46.5, 53.1, 67.0, 80.0, 129.2, 129.8, 135.0, 136.0, 156.0, 158.5, 171.0, 176.0; HRMS calcd for $C_{24}H_{38}N_4NaO_6$: 501.2689, found 501.2684 [M+Na]; IR: 1741, 1709, 1690, 1640 cm^{-1}.

Compound **7c**: Solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, J = 6.6 Hz, 3H), 1.86 (d, J = 4.3, 2H), 3.9 (t, J = 7.8 Hz, 1H), 4.2–4.43 (m, 4H), 4.52 (m, 2H), 5.32 (m, 2H), 6.1 (br, 2H), 7.2–8.1 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 21.2, 33.2, 37.3, 39.2, 42.4, 56.1, 121.0, 122.2, 124.5, 125.3, 126.0, 128.2, 128.3, 128.6, 129.4, 129.6, 131.2, 131.5, 135.0, 142.0, 156.0, 169.5, 172.4; HRMS calcd for $C_{35}H_{34}N_4NaO_6$: 629.2376, found: 629.2371 [M+Na]; IR: 1747, 1714, 1690, 1634 cm^{-1}.

Compound **8a**: White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91–0.95 (m, 12H), 1.33 (s, 9H), 1.58–1.62 (m, 2H), 2.41 (m, 4H), 3.81–3.92 (m, 3H), 4.18 (s, 2H), 5.45–5.6 (m, 3H), 6.9–7.4 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 19.5, 20.0, 21.0, 24.2, 28.4, 33.0, 37.1, 38.0, 44.9, 59.0, 66.5, 67.0, 122.0, 124.0, 128.5, 128.7, 129.3, 129.7, 130.0, 131.0, 157.0, 169.1, 169.7 170.0, 171.0; HRMS calcd for $C_{33}H_{45}N_5NaO_6$: 630.3268, found: 630.3271 [M+Na]; IR: 1696, 1645, 1634 cm^{-1}.

Compound **9b**: Solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89–0.93 (m, 12H), 1.39 (s, 9H), 1.71 (m, 2H), 2.53 (m, 2H), 3.9 (m, 4H), 4.3 (s, 2H), 5.42 (m, 3H), 7.1–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 19.4, 21.0, 23.2, 24.7, 32.0, 43.2, 47.0, 56.0, 59.0, 61.0, 77.0, 128.1, 128.7, 129.0, 129.5, 129.8, 154.0, 167.1, 167.8, 169.0, 171.1; HRMS calcd for $C_{26}H_{39}N_5NaO_6$: 540.2798, found: 540.2792 [M+Na]; IR: 1693, 1642, 1638 cm^{-1}.

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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.2008.06.091.

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24. *Note*: Several other reagents such as DAST, cyanuric fluoride, tetramethylfluoroformamidinium hexafluorophosphate (TFFH) and Mukaiyama's reagent are also used for the synthesis of acid fluorides, see: (a) Sureshbabu, V. V.; Gopi, H. N.; Ananda, K. *Indian J. Chem.* **2000**, *39B*, 384; (b) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 487.
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26. Deoxo-Fluor was used for the one-pot synthesis of Weinreb amides derived from Boc-Pro-OH, Boc-Leu-OH and Boc-Phe-OH via the corresponding acyl fluorides generated in situ using DIPEA. See: (a) Tunoori, A. R.; White, J. M.; Georg, G. I. *Org Lett.* **2000**, *2, 4091*. Similarly, Boc-Pro-NH_2 and Boc-Val-NH_2 were also prepared usingDeoxo-Fluor: (b) White, J. M.; Tunoori, A. R.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2004**, *69, 2573.*