ChemInform Abstract: Efficient Synthesis of N-Protected Amino/Peptide Weinreb Amides from T3P and DBU.

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Efficient synthesis of N-protected amino/peptide Weinreb amides from T3P and DBU

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The reaction of N\textsuperscript{3}-protected amino/peptide acid with N,O-dimethylhydroxylamine hydrochloride in the presence of T3P and DBU to obtain enantiomerically pure N\textsuperscript{3}-protected amino/peptidyl Weinreb amides in high yields has been described. Fmoc-Ala-Weinreb amide 2a is obtained as single crystal, and its structure was determined through X-ray crystallography.

A B S T R A C T

Weinreb amides\textsuperscript{1} have been employed as efficient and useful compounds for the preparation of ketones,\textsuperscript{2} aldehydes,\textsuperscript{3} acetylenes,\textsuperscript{4} heterocycles,\textsuperscript{5} natural products\textsuperscript{6} and also as a prolific moiety in Birch reductions and Wittig reactions as well.\textsuperscript{7,8} Recently Weinreb amides have been utilized in the synthesis of trifluoromethylketones.\textsuperscript{9} A specific class is the N-protected amino/peptide Weinreb amides, which are the key constituents for the preparation of unnatural amino acids and peptidomimetics.\textsuperscript{10} Classically, these derivatives have been synthesized by the treatment of N,O-dimethylhydroxylamine with an activated carboxylic group. Several peptide coupling reagents have been employed in this transformation which include BOP,\textsuperscript{11} DCC,\textsuperscript{12} DCC/HOBt,\textsuperscript{13} CBr\textsubscript{4}/Ph\textsubscript{3},\textsuperscript{14} EDC/HOBt,\textsuperscript{15} and CDMT.\textsuperscript{16} Additionally, mixed anhydride,\textsuperscript{17} acid chloride,\textsuperscript{18} acid fluoride\textsuperscript{19}, and acyl benzotriazoles\textsuperscript{20} methods have also been used under varied reaction conditions.

Some of these procedures are reported to be efficient, nevertheless, several limitations like poor yields, long coupling duration, harsh conditions, and tedious product isolation have evoked the search of efficient reagent system. Recently, 1-{[1-cyano-2-ethoxy-2-oxoethylideneaminoxy]-dimethylaminomorpholinomethyl}methanaminiumhexafluor phosphate (COMU)\textsuperscript{21} was employed to convert N-Boc-protected amino acids into the corresponding Weinreb amides in good yield and purity. As COMU is very expensive, it is less attractive for large scale preparations.

The recent demand for efficient and environmentally benign syntheses of fine chemicals and pharmaceuticals has lead to the development of mild and efficient synthetic reagents. In this respect from past decade the use of T3P (1-propanephosphonic acid cyclic anhydride) has experienced an exponential growth. The distinctive environmental benefits of T3P over other conventional reagents are due to its less toxicity, mild reaction conditions, broad functional group tolerance, high yields, less cost, low epimerization, and commercial availability. In addition, the formation of water soluble byproducts makes the isolation of the desired product simple and circumvents the use of volatile organic compounds (VOCs) during work-up. More importantly, T3P\textsuperscript{22} has experienced a renaissance as eco-friendly coupling reagent, which has been frequently described as most effective coupling reagent in the field of peptide chemistry.\textsuperscript{23} The advantages of T3P have been utilized in organic synthesis not only as coupling reagent but also as dehydrating agent and for various functional group interconversions that is, for the synthesis of nitriles, isonitriles, oxadiazoles, and thiadiazoles.\textsuperscript{24} Recently, T3P has been used as catalyst for the preparation of polysubstituted quinolines\textsuperscript{25} and for the synthesis of fused heterocycles.\textsuperscript{26} Our group has reported the Curtius\textsuperscript{27a} and Lossen rearrangements mediated by T3P.\textsuperscript{27b} Also, T3P has been employed for the synthesis of N\textsuperscript{\textsuperscript{\textsuperscript{3}}}-protected aminothio acids\textsuperscript{27c} and \(\beta\)-\ and \(\gamma\)-amino alcohols.\textsuperscript{27d} In continuation of our interest on the utility of T3P, we herein describe the synthesis of enantiomerically enriched N-protected \(\alpha\)-amino/peptide pure Weinreb amides mediated by T3P under mild conditions and the results are summarized herein.

A thorough literature survey on the T3P mediated Weinreb amide preparations revealed that, side chain \(\gamma\)-COOH of N-Boc-Glu-OMe was converted into respective Weinreb amide by the treatment of T3P and N-ethylmorpholine (NEM). Initially, we
sought to reinvestigate the synthesis of Weinreb amide 2a derived from Fmoc-Ala-OH 1a following this literature protocol.28 The same reaction conditions failed to give good yield of 2a (Table 1, entry 1) in 30 min. Consequently, we examined the ability of various bases to promote the reaction of 1a with T3P and N,O-dimethylhydroxylamine at 0 °C. The reaction progress was monitored by the TLC. DMAP and imidazole failed to give the expected product in 40 min (Table 1, entries 2 and 3). The use of TEA, NMM, and pyridine (Table 1, entries 4–6) gave satisfactory yields of 2a after 35 min. However, isolation of the pure product required column purification which precludes the choice of base. The amidine type base DBU has been found to be more effective than traditional tertiary organic bases in several organic reactions.29 Its high basicity is attributed by the resonance-stabilized cations. Because of the Lewis basic properties (non-nucleophillic) DBU has also been used as efficient catalyst in organic synthesis.29 Recently, we have demonstrated the efficacy of DBU for the synthesis of ureas.30 To test the scope of DBU in the present reaction, we carried out the reaction of 1a and N,O-dimethylhydroxylamine at 0 °C in the presence of T3P and DBU (Table 1, entry 7). After 30 min, TLC examination confirmed that the reaction was found to be complete. A simple aqueous work-up of the reaction mixture resulted in the isolation of the product 2a in high yield and purity (>98% conversion as confirmed by HPLC analysis). Similar study was undertaken to determine if solvent played a significant role in the reaction outcome. It was found that CH3CN provided best result in terms of yield and purity to other solvents including THF, DMF, DMSO, toluene, and CH2Cl2 (Table 1, entries 8–12). Additionally, we carried out the reaction of 1a with T3P and N,O-dimethylhydroxylamine in the presence of NEM as a base in CH3CN (Table 1, entry 13). Comparison of the results obtained in entries 1 and 13 suggested that yields were also influenced by the solvent and the good yield was obtained in CH3CN.

Exploring the scope of the optimized reaction conditions, we further synthesized a series of compounds 2b–p (Scheme 1).31

Table 1
Optimization of reaction conditions for the synthesis of 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NEM</td>
<td>THF</td>
<td>71a</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>DMAP</td>
<td>CH3CN</td>
<td>—</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>Imidazole</td>
<td>CH3CN</td>
<td>—</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>NMM</td>
<td>CH3CN</td>
<td>79c</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>TEA</td>
<td>CH3CN</td>
<td>81c</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>Pyridine</td>
<td>CH3CN</td>
<td>83c</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>DBU</td>
<td>CH3CN</td>
<td>97c</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>DBU</td>
<td>DMSO</td>
<td>75c</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>DBU</td>
<td>DMF</td>
<td>80c</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>DBU</td>
<td>THF</td>
<td>69c</td>
<td>35</td>
</tr>
<tr>
<td>11</td>
<td>DBU</td>
<td>Toluene</td>
<td>71c</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>DBU</td>
<td>CH2Cl2</td>
<td>78c</td>
<td>35</td>
</tr>
<tr>
<td>13</td>
<td>NEM</td>
<td>CH2CN</td>
<td>80c</td>
<td>30</td>
</tr>
</tbody>
</table>

a 1.1 equiv of NHMe(OMe)HCl in 1.1 equiv of TEA was used.
b Reported reaction conditions were maintained.
c Isolated yield after column purification.
d Yields of the crude product after work-up followed by triturating with ether.

Scheme 1. Synthesis of Nα-protected amino acid derived Weinreb amides.

Table 2
List of Nα-Fmoc/Boc/Cbz-protected amino acid Weinreb amides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product 2</th>
<th>[α]25°b</th>
<th>Yielda (%)</th>
<th>Entry</th>
<th>Product 2</th>
<th>[α]25°b</th>
<th>Yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>FmocHN</td>
<td>−12.4</td>
<td>97</td>
<td>i</td>
<td>BocHN</td>
<td>−19.1</td>
<td>91</td>
</tr>
<tr>
<td>b</td>
<td>FmocHN</td>
<td>+18.2</td>
<td>98</td>
<td>j</td>
<td>CbzHN</td>
<td>−20.2</td>
<td>89</td>
</tr>
<tr>
<td>c</td>
<td>Ph</td>
<td>−18.3</td>
<td>91</td>
<td>k</td>
<td>CbzHN</td>
<td>−28.2</td>
<td>99</td>
</tr>
<tr>
<td>d</td>
<td>BocHN</td>
<td>−15.6</td>
<td>90</td>
<td>l</td>
<td>BocHN</td>
<td>−26.2</td>
<td>91</td>
</tr>
<tr>
<td>e</td>
<td>FmocHN</td>
<td>−25.1</td>
<td>92</td>
<td>m</td>
<td>FmocHN</td>
<td>−38.1</td>
<td>94</td>
</tr>
</tbody>
</table>

(continued on next page)
The products were isolated by a simple work-up followed by triturating with ether. As furnished in Table 2, yields are good in all cases (89–99%). The method is compatible with commonly used N-urethane protecting groups, different side chain functionalized amino acids (Ser, Tyr, Thr, Lys, and Glu) and sterically hindered amino acids (Ile and Aib) as well. The RP-HPLC analysis of crude product 2c (>98% purity) revealed the good purity of the products (Fig. 1d).

Further, several N-protected di and tri-peptide derived Weinreb amides 4a–g were also synthesized (Scheme 2) and have been obtained in good yields (Table 3). The structural assignment of the Weinreb amides 2 and 4 were also synthesized (Scheme 2) and have been obtained in good yields (Table 3). The optical rotational data obtained for all samples showed that no racemization of the chiral center on the α-carbon atom occurred during the synthesis. Also, these values are in consistent to the reported ones in the literature. The chiral HPLC analysis was carried out for enantiomeric pair of Fmoc-L-Ala-Weinreb amide 2a and Fmoc-D-Ala-Weinreb amide 2b and intentionally prepared D, L mixture. The samples 2a (Fig. 1a) and 2b (Fig. 1b) had single distinct peak with retention values at Rₜ 11.01 and 15.50, respectively. Also an intentionally made equimolar mixture of 2a and 2b showed a significant difference in the retention times between D and L amino acid derivatives (Fig. 1c, retention times for the racemic amides derived from 2a and 2b were Rₜ 11.3 and 15.1 min). These studies confirmed that the present protocol is free from racemization.

During the course of this study Fmoc-Ala-Weinreb amide 2a (CCDC No. 900995) was obtained as single crystal and the molecular structure was determined through X-ray crystallography. Two literature precedents were found on the crystal structure analysis of amino acid derived Weinreb amides. Zheng et al. reported the crystal structure of racemic Boc-L-phenylalanyl N-methoxy-N-methylamide. Thomas Kolter has reported the crystal structure of aminoalicyclic acid derived Weinreb amide. In the present study, the crystals of Weinreb amide 2a suitable for X-ray analysis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product 2</th>
<th>[α]D21b (°)</th>
<th>Yielda (%)</th>
<th>Entry</th>
<th>Product 2</th>
<th>[α]D21b (°)</th>
<th>Yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>f</td>
<td>FmocHN</td>
<td>−14.5</td>
<td>89</td>
<td>n</td>
<td>BocN</td>
<td>−37.1</td>
<td>89</td>
</tr>
<tr>
<td>g</td>
<td>FmocHN</td>
<td>−16.7</td>
<td>90</td>
<td>o</td>
<td>FmocHN</td>
<td>−</td>
<td>75</td>
</tr>
<tr>
<td>h</td>
<td>BocHN</td>
<td>−13.9</td>
<td>94</td>
<td>p</td>
<td>CbzHN</td>
<td>−25.6</td>
<td>93</td>
</tr>
</tbody>
</table>

* Isolated yield.

Figure 1. (a) Chiral HPLC profile of 2a. (b) Chiral HPLC profile of 2b. (c) Chiral HPLC of racemic mixture of 2a and 2b. (d) RP-HPLC of crude product 2c.
were grown by layering of a THF solution with hexane. The crystal structure reveals that orthorhombic non-centrosymmetric space group $P2_12_12_1$ with $Z = 4$. The crystal structure is mainly stabilized by strong N–H···O bonds along with weak C–H···O bonds. An ORTEP diagram depicted in Figure 2 shows the molecular structure, the asymmetric unit, and intra and intermolecular H-bonding. The details of the selected bond lengths, bond angles, and torsion angle values for compound 2a are given in Supplementary data.\textsuperscript{37}

In conclusion a simple and modular procedure has been described for the preparation of a series of N-protected z-amino peptide Weinreb amides by employing combination of T3P and DBU. The use of mild conditions enables the isolation of the products without racemization. The Weinreb amide 2a was obtained as single crystal and the molecular structure has been confirmed through X-ray crystallography.

Acknowledgments

We gratefully acknowledge the Board of Research in Nuclear Sciences (Grant No. 2011/37C/35/BRNS), Govt. of India for the financial assistance. M.S.K. thanks the DST Govt. of India for the award of an INSPIRE fellowship. We thank Dr. H.N. Gopi, IISER, Pune for X-ray crystallographic analysis. We also thank Archimica GmbH, Industrial park, Hochst Building D56965926, Frankfurt am Main, Germany for providing 50% T3P in EtOAc as gift sample.

Supplementary data

Supplementary data (crystallographic data for compound Fmoc-Ala-Weinreb amide 2a (CCDC No.900995)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.064.

References and notes


40. Sureshbabu, V. V.; Basavaprabhur: Synlett 2011, 1160.
41. General procedure for the synthesis of N-Fmoc/BOC/O-/-amino/peptide/Weinreb amides 2 and 4: To a solution of N-protected amino/peptide/Weinreb amides 2 and 4 in CH2Cl2 (2.0 mL), DMSO (1 mmol, 0.16 mL), and T3P (50% in ETOAc, 1.02 mL, 3.2 mmol) were added at 0 °C and the solution was stirred for about 1.5 h. Then, N,N-dimethylhydroxylamine (1.1 mmol, 0.11 g hydrochloride salt was neutralized by the addition of 1.1 mmol, 0.12 mL TEA) was added to the reaction mixture and the reaction was allowed to stir till the completion of the reaction as indicated by TLC. After the evaporation of solvent, the crude product was extracted into EtOAc and the organic phase was washed with 5% citric acid (10 mL x 2), 5% Na2CO3 (10 mL x 2), water and brine solution and dried over anhydrous Na2SO4. The solvent was evaporated and the product was isolated after following by triturating with ether.
42. HPLC particulars: Agilent 1100 series having G1311A VWD at λ = 254 nm, flow 0.5 mL/min, Column: Agilent Eclipse XDB-C18, pore size: 5 μm, diameter × length = 4.6 × 150 mm; Method: gradient 0.1% TFA water-acetonitrile: acetonitrile 30–100% in 30 min.
43. Spectroscopic data: N2-Fmoce-Athr-OMe/Me (2a): White solid (86%); mp 113 °C; IR (KBr): 1725, 1662 cm–1; 1H NMR (300 MHz, CDC13) δ 1.23 (d, J = 7.2 Hz, 3H), 3.13 (3H), 3.65 (3H, 4.21 (t, J = 5.8 Hz, 1H), 4.48 (d, J = 9.1 Hz, 2H), 4.59 (m, 1H), 5.51 (d, J = 5.2 Hz, 1H), 7.25–7.77 (m, 8H); 13C NMR (75 MHz, CDC13) δ 17.2, 32.0, 43.1, 46.2, 60.6, 66.5, 125.8, 127.1, 127.6, 128.1, 139.5, 140.9, 153.6, 155.8; HRMS: m/z [M+Na]⁺ calcd for C15H22N2O4: 317.1477, found 317.1477.
44. N2-Fmoce-Phe-Leu-OMe/Me (4a): White solid (81%); mp 118 °C; IR (KBr): 1706, 1665 cm–1; 1H NMR (300 MHz, CDCl3) δ 0.98 (d, J = 6.9 Hz, 6H), 1.42 (m, 2H), 1.78 (m, 1H), 2.98 (m, 1H), 3.11 (m, 1H), 3.16 (s, 3H), 3.58 (s, 3H), 4.18 (t, J = 7.5 Hz, 1H), 4.45 (d, J = 12.5, 2H), 4.54 (d, J = 3.9 Hz, 2H), 4.71 (m, 1H), 5.51 (d, J = 5.5 Hz, 1H), 6.11 (s, br, 1H), 7.11–7.59 (m, 13H); 13C NMR (75 MHz, CDCl3) δ 20.8, 21.4, 30.8, 36.3, 39.2, 43.5, 45.9, 53.6, 59.8, 65.1, 120.1, 125.2, 125.8, 127.0, 127.6, 128.2, 128.5, 138.6, 140.9, 140.3, 155.5, 155.9, 170.6; HRMS: m/z [M+Na]⁺ calcd for C15H22N2O4Na+: 566.2631; found 566.2622.
45. N2-Czb-Val-N(Oe)Me/Me (2b): Isolated as white solid (99%); mp IR (KBr): 1715, 1650 cm–1; 1H NMR (300 MHz, CDCl3) δ 0.99 (d, J = 10.6 Hz, 6H, 2.25 (m, 1H), 3.19 (s, 3H), 3.58 (s, 3H), 4.21 (d, J = 7.9 Hz, 1H), 5.43 (s, 7H), 7.12 (s, 1H; 13C NMR (75 MHz, CDC13) δ 17.8, 30.2, 32.0, 53.6, 60.1, 64.6, 127.0, 128.1, 128.4, 139.5, 153.4, 145.2; HRMS: m/z [M+Na]⁺ calcd for C15H24N2O3Na+: 537.1477; found 537.1468.
46. N2-Boc-Asp(Oa)-N(Oe)Me/Me (3b): Isolated as colorless oil (94%); IR (neat): 1722, 1753 cm–1; 1H NMR (300 MHz, CDCl3) δ 1.32 (s, 9H), 3.21 (s, 3H), 2.61–2.75 (m, 2H), 3.18 (s, 3H), 3.51 (s, 3H), 4.36 (m, 1H, 4.72 (s, br, 1H; 13C NMR (75 MHz, CDCl3) δ 28.3, 28.5, 32.2, 49.4, 50.9, 60.8, 78.4, 152.2, 170.3, 173.4; HRMS: m/z [M+Na]⁺ calcd for C15H24N2O4Na+: 313.1478; found 313.1462.
47. Chiral PLC particulars: Agilent 1100 series having G1311A VWD at λ = 254 nm, flow 1.0 mL/min, Column: Phenomex made Lux, pore size: 5 μm, Cellulose-1, diameter × length = 250 × 46 mm; Method: 80:20 6-hexane-isopropanol in isocratic mode in 40 min.
50. CCDC No. 900995 contains the supplementary crystallographic data for compound 2a. These data can be obtained for free of charge from the Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/datarequest cif.