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Orthogonally Protected Imidazolidine-2-Carboxylic Acid, a new Proline Surrogate suitable for SPPS.

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Abstract : N-Boc-N'-Fmoc-imidazolidine-2-carboxylic acid, easily prepared from N-Boc-N'-Fmoc-ethylenediamine and glyoxylic acid, is a racemic proline surrogate which can be used in Solid Phase Peptide Synthesis.

Differentially protected α-aminoglycines, in particular N-α-Boc-N-α'-Fmoc-diaminoacetic acid, is a promising building block that can be used in the synthesis of α-aminoglycine containing peptides by solid phase peptide synthesis[1]. Whereas selective acylation of one amino group turned out to be a good strategy to provide access to "betidaminoacid" containing polymers, introduction of an alkyl group at the same position has met with little success so far[2]. In the course of a search for a general solution to this synthetic problem, we especially looked for the methods susceptible to afford a N,N'-disubstituted diaminoacetic acid as a proline equivalent, suitable for SPPS which would be useful for generation of molecular diversity in combinatorial chemistry. Since the approach optimized[3] for the synthesis of N-α-Boc-N-α'-Fmoc-diaminoacetic acid was unsuccessful, new conditions were systematically investigated to obtain differentially protected imidazolidine-2-carboxylic acids.

N,N'-diphenyl ethylenediamine was previously reported to give 1,3-diphenyl imidazolidine-2-carboxylic acid upon condensation with glyoxylic acid in alcohol[4]. Similarly, 1,3-dibenzoyl imidazolidine was isolated in modest yield upon reaction of ethylenediamine with aqueous formaldehyde followed by acylation with benzoyl chloride[5]. Finally, 2-alkyl imidazolidines were prepared upon reaction of ethylenediamine with alkylvinylethers in the presence of mercuric benzoate[6].

We have found that N-acetyl-N'-Boc-imidazolidine-2-carboxylic acid **3a**[7], N-Boc-N'-Z-imidazolidine-2-carboxylic acid **3b**[8] and N-Boc-N'-Fmoc-imidazolidine-2-carboxylic acid **3c**[9] are easily obtained using glyoxylic acic monohydrate with N-acetyl-N'-Boc ethylenediamine **1a**, N-Boc-N'-Z-ethylenediamine **1b**[10], and N-Boc-N'-Fmoc-ethylenediamine **1c**[11], respectively, in acetic acid at 60°C (Scheme 1).

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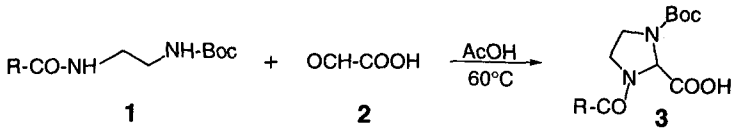

a: R = CH_3, **b**: R = Benzyloxy, **c**: R = Fluorenylmethyloxy

Scheme 1

Using the pentafluoro-phenyl ester of compound **3c,** the racemic proline surrogate could easily be incorporated into a peptide using the Fmoc-based solid phase synthesis strategy as exemplified by the synthesis of the octapeptide V-S-Q-N-F-(2-imidazolidinyl)-I-V-OH[12] overlapping the Matrix-Capsid cleavage site of the HIV-1 protease natural substrate[13].

References and notes

Abbreviations: Boc: *t*-butyloxycarbonyl; Fmoc: 9-fluorenylmethyloxycarbonyl; Z: benzyloxycarbonyl; SPPS: Solid Phase Peptide Synthesis; TFA: trifluoroacetic acid.

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7. **3a**: yield 77%; mp = 118 °C; RMN ^1H (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.11, 2.19 (s, 3H), 3.70 (m, 4H), 5.70 (m, 1H), 9.63 (bs, 1H); RMN ^{13}C (75 MHz, $CDCl_3$) δ 21.71, 22.18, 28.27, 28.33, 28.42, 43.61, 44.14, 45.76, 69.70, 70.56, 82.24, 169.53, 176.8; Mass spectroscopy (chemical ionization, isobutane) m/z 259 (M+H), 203 (M+H -isobuten), 159 (M+H -Boc);
8. **3b**: yield 87%; RMN ^1H (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 3.70 (m, 4H), 5.14 (m, 2H), 5.58 (bs, 1H), 7.32 (bs, 5H), 9.45 (bs, 1H), 13.3 (b, 1H); RMN ^{13}C (75 MHz, $CDCl_3$) δ 28.30, 44.31, 68.11, 69.76, 82.14, 128.21, 128.65, 135.78; Mass spectroscopy (chemical ionization, isobutane) m/z 351 (M+H), 295 (M+H -isobuten), 251 (M+H -Boc).
9. **3c**: yield 74% ; mp = 168-169 °C; RMN ^1H (300 MHz, DMSO-d_6) δ 1.52 (s, 9H), 3.71 (m, 4H), 4.39 (m, 1H), 4.45 (m, 2H), 5.45 (m, 1H), 7.44 (m, 2H), 7.51 (m, 2H), 7.80 (d, 2H), 8.02 (d, 2H); RMN ^{13}C (75 MHz, DMSO-d_6) δ 28.42, 44.48, 47.08, 67.86, 70.16, 80.84, 120.58, 125.74, 127.69, 128.29, 141.29, 144.10, 144.16, 153.45, 170.63; Mass spectroscopy (chemical ionization, isobutane) m/z 439 (M+H), 383 (M+H -isobuten), 339 (M+H -Boc); **Pentafluorophenyl ester of 3c**: Mass spectroscopy (chemical ionization, isobutane) m/z 605 (M+H), 549 (M+H -isobuten), 505 (M+H -Boc).
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