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Facile synthesis and cleavage of imidazolidines in a novel protection strategy for the preparation of peptides containing a reduced amide bioisostere

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Abstract—Unsymmetrical imidazolidines were obtained in 75–91% yield by treating monoalkoxycarbonyl vicinal diamines at room temperature with aqueous 37% formaldehyde in the presence of Montmorillonite KSF as a solid catalyst. The imidazolidines were shown to be useful intermediates in a novel protection strategy for the synthesis of peptide analogues containing a reduced glycine amide bioisostere. The imidazolidine intermediate was cleaved conveniently and efficiently by 50% TFA in methylene chloride.

Imidazolidine, a fully saturated imidazole heterocycle, is an important intermediate and building block in the construction of a variety of biologically active compounds.[1–3] Its vicinal diamine functionality is of great interest in organic chemistry as a chiral auxiliary or a metal ligand in catalytic asymmetric synthesis and in medicinal chemistry as a component of various drugs.[2] The hydrophobic nature of imidazolidines can be used to increase the bioavailability of biologically active precursors in the form of a prodrug.[3]

A number of methods have been described in the literature for the preparation of symmetrical imidazolidines including condensation of vicinal diamines with formaldehyde using a Dean–Stark apparatus or activated molecular sieves to remove water,[4] treatment of diamines with paraformaldehyde or benzaldehyde in chloroform in the presence of anhydrous $MgSO_4$ and K_2CO_3,[5] reduction of symmetrical cyclic urea with $LiAlH_4$,[6] condensation of diamines with benzotriazole and formaldehyde via a Mannich reaction followed by substitution with a Grignard reagent,[7] and condensation of acid-sensitive aldehydes containing furan and pyrrole with diamino compounds in refluxing benzene.[8] Despite the availability of these methods for the synthesis of symmetrical imidazolidines, relatively few papers have been published describing the preparation of unsymmetrical imidazolidines.[9–12] Kliegel and Franckenstein prepared unsymmetrical imidazolidines by condensation of aldehydes with vicinal diamines obtained via a low-yielding S_N2 reaction.[9] Lambert and co-workers reported the synthesis via two sequential reactions of diethyl oxalate with 1 equiv. of two different primary amines followed by reduction with $LiAlH_4$ and condensation with formaldehye.[10] The overall yield of this synthesis, however, was only about 25%. Perillo et al. prepared 1-benzyl-*N*-arylimidazolidines via a three-step process: condensation of haloalkylamides with primary aromatic amine followed by reduction with borane in refluxing THF and condensation with an aldehyde.[11] Katritzky recently prepared imidazolidines by a Mannich reaction of diamines with benzotriazole and formaldehyde, followed by the nucleophilic substitution with a C-nucleophile.[12] Herein, we report a simple, efficient method for the formation of unsymmetrical imidazolidines using Montmorillonite KSF clay as a solid catalyst and the application of using imidazolidine as a protection strategy in the synthesis of peptide analogues containing a reduced amide bioisostere.

During our synthesis of peptides containing a reduced glycine amide bioisostere using reductive alkylation of monoalkoxycarbonyl diamine (**1**→**2**, Scheme 1), we identified the formation of the unsymmetrical imidazolidine **3** as a by-product in 5% yield. After evaluating several literature procedures on the formation of imidazolidines,[4,5,8] we tried to form imidazolidine **3** by condensation of **1** with aqueous 37% formaldehyde in the

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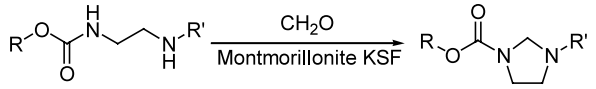
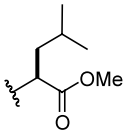
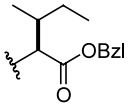
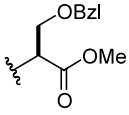
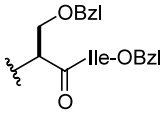
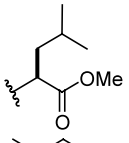
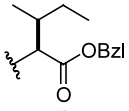
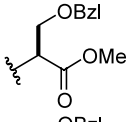
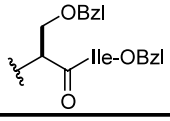
Table 1. Formation of unsymmetrical imidazolidines from monoalkoxycarbonyl vicinal diamines[a]

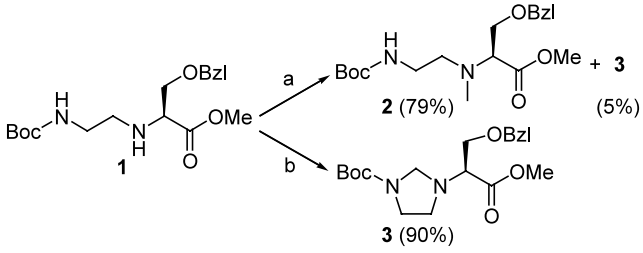


Entry	R	R'	Time (h)	Yield (%)[b]
1	*t*-But		2.5	91
2	*t*-But		2.0	86
3	*t*-But		1.5	90
4	*t*-But		4.0	91
5	Fm		1.5	80
6	Fm		2.0	75
7	Fm		1.5	81
8	Fm		4.5	82

[a] All compounds were confirmed by NMR and LC-MS.
[b] Isolated yields.

absence of the reducing agent. Unfortunately, the yields were always low (~50%). The importance of imidazolidines in organic and medicinal chemistry in addition to its potential application as a protection strategy prompted us to develop a new set of conditions for the efficient synthesis of unsymmetrical imidazolidines.

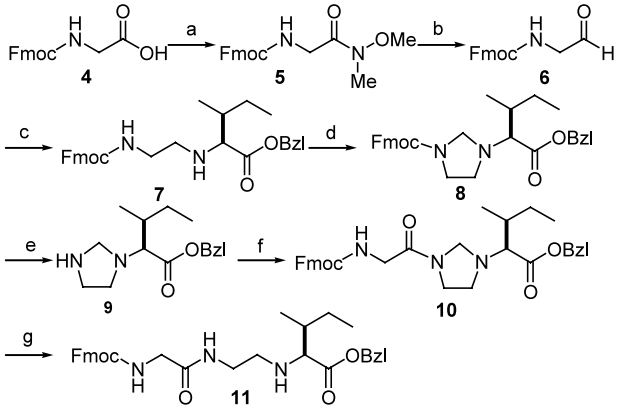
Recently, inorganic solids have gained popularity as solid catalysts in a variety of organic transformations. For example, solid clay has been shown to function as a catalytically active agent, as a bifunctional or 'inert' support, and as a filler to give solid catalysts the required physical properties.[13] We decided to test the feasibility of using Montmorillonite KSF as a solid catalyst in the formation of unsymmetrical imidazolidines. It was found that monoalkoxycarbonyl vicinal diamine **1** was converted easily to its corresponding imidazolidine **3** in high yield (90%) at room temperature upon treatment with aqueous 37% formaldehyde in the presence of Montmorillonite KSF (400 mg per mmole of the diamine).[14,15] Table 1 lists the unsymmetrical imidazolidines synthesized from monoalkoxycarbonyl vicinal diamines, reaction times, and yields. The reaction was complete between 1.5 and 4 h under our mild conditions with yields between 75 and 91%.



Scheme 1. *Reagents and conditions:* (a) CH_2O, $NaBH(OAc)_3$; (b) CH_2O, Montmorillonite KSF.

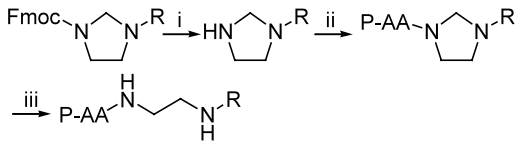
Since imidazolidine ring is known to be unstable under acidic conditions and easily reverts back to its corresponding vicinal diamine, we envisioned that it might be useful as an important intermediate in the temporary protection of the secondary amine in vicinal diamines in peptide synthesis. Here, Fmoc chemistry would be used instead of Boc to achieve an orthogonal protection scheme between the *N*-terminal amine protection and imidazolidine.

Scheme 2 illustrates the use of imidazolidines as a protection strategy during the synthesis of peptide analogues containing a reduced glycine amide bioisostere. Fmoc-glycine (**4**) was converted to its corresponding aldehyde **6** through the Weinreb amide **5**.[16] Aldehyde **6** was then used to reductively alkylate isoleucine benzyl ester in the presence of the reducing agent sodium triacetoxyborohydride to give the vicinal diamine Fmoc-Gly-ψ[CH_2NH]-Ile-OBzl (**7**). Compound **7** was

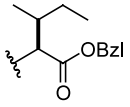
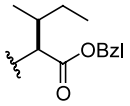
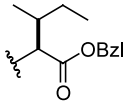
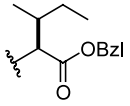
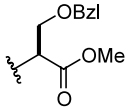
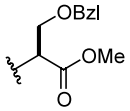
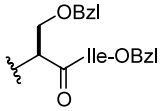
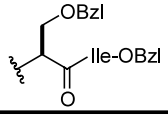


Scheme 2. *Reagents and conditions:* (a) HOBt, EDC, MeONHMe, 94%; (b) $LiAlH_4$, anhydrous THF/DMF (5:1), 85%; (c) H–Ile–OBzl, Montmorillonite KSF, anhydrous THF; then $NaBH(OAc)_3$, 79%; (d) formaldehyde (37% aqueous solution), Montmorillonite KSF, anhydrous THF, 75%; (e) 20% piperdine/CH_2Cl_2, 20 min; (f) Fmoc-Gly-OH, HATU, DIEA, CH_2Cl_2/NMP (10:1), yield 63% (two steps from **8**); (g) 50% TFA/CH_2Cl_2, 2 h, 100%.

Table 2. Peptide analogues containing a reduced amide bioisostere synthesized in 3 steps from imidazolines[a]



Reagents and conditions: i) 20% piperidine/CH_2Cl_2; ii) P-AA-OH, HATU, DIEA, CH_2Cl_2/NMP; iii) 50% TFA/CH_2Cl_2

Entry	P-AA	R	Yield (%)[b]
1	Fmoc-Gly		63
2	Fmoc-Arg		65
3	Cbz-Gly		66
4	Cbz-Leu		69
5	Cbz-Ala		69
6	Fmoc-Arg		56
7	Fmoc-Gly		59
8	Fmoc-Arg		65

[a] All compounds were confirmed by NMR and LC-MS.
[b] Isolated yields, three steps combined: i) Fmoc deprotection, ii) amino acid coupling, iii) imidazolidine cleavage

treated with aqueous 37% formaldehyde in the presence of Montmorillonite KSF as a catalyst to yield the imidazolidine **8** in 75% yield.[17] Selective removal of the Fmoc protecting group with 20% piperidine in methylene chloride afforded imidazolidine **9** with a free secondary amine. After removing all solvents and excess piperidine by a Speed Vac, compound **9** was coupled to Fmoc-Gly-OH with HATU as the activating agent to yield compound **10**. After purification by flash column chromatography, the imidazolidine ring was cleaved by treatment with 50% TFA in methylene chloride to produce the desired peptide analog Fmoc-Gly-Gly-ψ[CH_2NH]-Ile-OBzl (**11**) in quantitative yield.[18]

It is important to note that after Fmoc deprotection, imidazolidine **9** was not very stable and was subjected to amino acid coupling without further purification. Also, excess piperidine must be removed completely, otherwise it would affect the next coupling reaction. Other reagents such as TBAF can also be used for the selective deprotection of Fmoc in place of piperidine.[19] As shown in Table 2, a number of peptide analogues containing a reduced glycine amide bioisostere were synthesized using the strategy outlined in Scheme 2 in good overall isolated yields ranging from 56 to 68% for the three steps of Fmoc deprotection, amino acid coupling, and imidazolidine ring cleavage. Pmc was used as a protecting group of side chain guanidinium group in the synthesis of arginine-containing peptide analogues (entries 2, 6, and 8). The acid treatment used to open the imidazolidine ring also cleaved the Pmc protecting group.

In conclusion, a simple, efficient method was developed for the formation of unsymmetrical imidazolidines by employing Montmorillonite KSF clay as a solid catalyst. We have demonstrated that imidazolidines could be used as an important intermediate in the synthesis of peptide analogues containing a reduced glycine amide bioisostere. Cleavage of the imidazolidine ring was effected conveniently and efficiently using 50% TFA in methylene chloride. The same strategy might also be applied to the synthesis of peptide analogues containing other reduced amides.[20]

Acknowledgements

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14. Typical procedure for the formation of imidazolidines: To a solution of substrate monoalkoxycarbonyl diamine (1 mmol) in anhydrous THF (5 mL) was added at room temperature Montmorillonite KSF (400 mg) followed by aqueous 37% formaldehyde (3 mmol). The reaction mixture was stirred at room temperature for 1 h or until the starting material disappeared as monitored by TLC. After filtration, the solvent was removed in vacuo and residue was subjected to flash column chromatography to afford the desired imidazolidine.
15. Spectroscopic data for compound **1**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm 1.46 (s, 9H), 2.54 (br s, 1H), 2.62 (m, 2H), 3.20 (m, 2H), 3.48 (t, $J=4.8$ Hz, 1H), 3.68 (d, $J=4.8$ Hz, 2H), 3.73 (s, 3H), 4.54 (s, 2H), 5.01 (br s, 1H), 7.29 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm 28.4, 40.3, 47.4, 60.9, 70.6, 73.2, 79.0, 127.6, 127.8, 128.4, 137.8, 141.4, 156.2, 173.2. LC–MS (ESI^+) m/z (relative intensity): 353.6 ($M+H^+$ 100%), 705.7 ($2M+H^+$, 24%);
For compound **3**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm 1.46 (s, 9H), 3.00 (m, 2H), 3.43 (m, 2H), 3.54 (m, 1H), 3.75 (s, 3H), 4.12 (m, 1H), 4.21 (m, 1H), 4.56 (s, 2H), 7.33 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm 28.5, 43.8, 49.4, 52.0, 63.7, 65.1, 69.2, 73.4, 79.6, 127.8, 127.9, 128.5, 137.6, 153.4, 170.8. LC-MS (ESI^+) m/z (relative intensity): 365.4 ($M+H^{+\cdot}$ 100%), 387.4 ($M+Na^+$, 28%).
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18. Spectroscopic data for compound **10**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm 0.90–1.00 (m, 6H), 1.24 (m, 2H), 1.84 (m, 1H), 3.06 (m, 1H), 3.20 (m, 1H), 3.57 (m, 3H), 3.90 (dd, 2H, $J=4.4$, 12.8 Hz), 4.12 (t, 1H), $J=10.5$ Hz), 4.36 (m, 2H), 4.44 (m, 2H), 5.18 (s, 2H),5.78 (br s, 1H), 7.38 (m, 9H), 7.64 (d, 2H, $J=10.8$ Hz), 7.79 (d, 2H, $J=10.8$ Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm 11.0, 15.5, 25.9, 29.8, 35.3, 43.5, 47.3, 48.9, 64.4, 66.5, 67.3, 67.9, 120.0, 125.2, 127.2, 127.8, 128.6, 128.7, 128.8, 129.0, 129.8, 135.5, 141.4, 144.0, 156.3, 165.7, 171.3. LC-MS (ESI^+) m/z (relative intensity): 556.2 ($M+H^+$, 100%), 578.2 ($M+Na^+$, 12%).
For compound **11**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm 0.90–1.00 (m, 6H), 1.28 (m, 2H), 2.07 (m, 1H, NH), 2.46 (m, 2H), 2.90 (m, 2H), 3.45 (m, 2H), 3.68 (m, 2H), 4.22 (t, 1H, $J=10.5$ Hz), 4.36 (m, 2H), 4.44 (m, 2H), 5.18 (s, 2H), 5.22 (br s, 2H, CONH), 7.28–7.37 (m, 9H), 7.64 (d, 2H, $J=10.8$ Hz), 7.79 (d, 2H, $J=10.8$ Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ ppm 11.6, 14.1, 26.6, 29.8, 36.4, 36.7, 47.0, 49.9, 65.0, 67.8, 68.6, 120.1, 125.2, 127.2, 127.9, 128.9, 129.2, 141.4, 143.4, 156.3, 165.4, 176.2. LC–MS (ESI^+) m/z (relative intensity): 544.2 ($M+H^+$, 100%), 566.2 ($M+Na^+$, 20%).
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