The Synthesis of Aminoazole Analogs of Lysine and Arginine: The Mitsunobu Reaction with Lysinol and Argininol

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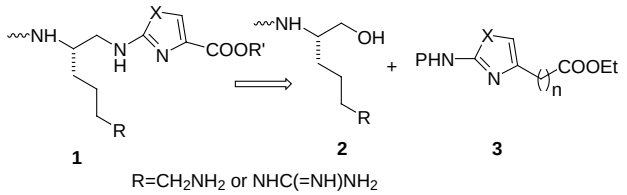
Abstract: The Mitsunobu reaction of aminooxazoles and thiazoles with lysinol and argininol is described. The aminooxazoles and thiazoles reacted with lysinol or argininol in the presence of triphenylphosphine and dialkyl azodicarboxylate to provide the reduced peptidyl azoles in moderate to good yields.

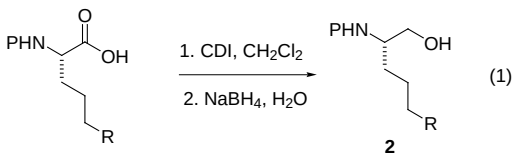
Key words: Mitsunobu reaction; aminooxazole; aminothiazole; reduced peptidyl azoles; peptide isostere; thrombin inhibitor

As part of our continuing investigations in the development of anticoagulants,[1] we needed a method to prepare reduced dipeptidyl azoles **1**. We envisaged that it could be constructed from an *N*-protected lysinol or argininol moiety **2** and an aminoazole ester **3** (Scheme 1).



Scheme 1

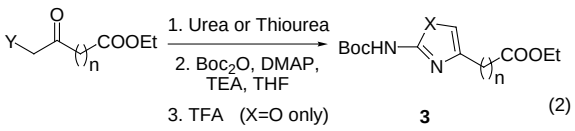
Although there are several known methods to prepare amino alcohols **2** from amino acids,[2] several are problematic, affording low yields and/or tedious reaction procedures. To this end, we utilized 1,1'-carbonyldiimidazole (CDI) to activate the *N*-protected lysine or arginine and subsequently reduced the acylimidazolide with $NaBH_4$ to provide the corresponding *N*-protected amino alcohols **2a-d** in good yields[3] (Eq. 1). This CDI-modification affords a simple and facile reduction of *N*-protected lysine or arginine.



(1)

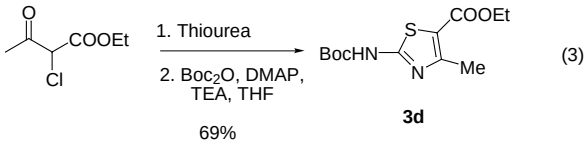
2a: P=Boc, R=CH_2NHCbz, 100%
2b: P=Fmoc, R=CH_2NHBoc, 88%
2c: P=Boc, R=NHC(=NH)NHCbz, 76%
2d: P=Boc, R= HC(=NCbz)NHCbz, 90%

The aminoazole moiety **3** was synthesized by the reaction of thiourea or urea with the corresponding halooxo esters in ethanol, followed by protection to provide the desired ethyl 2-(*N*-Boc)amino-4-azole esters **3a-d** in good yields[4] (Eq. 2 and 3). In the case of the aminooxazole **3c**, the ethyl 2-(N,N'-bis-Boc)amino-4-oxazole carboxylate was formed during the addition of the Boc group, however treatment with an equivalent of TFA[5] was sufficient to convert it to the desired mono-Boc aminooxazole.



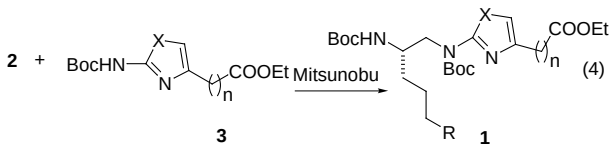
(2)

3a: n=0, X=S (Y=Br, 85%) **3b**: n=1, X=S (Y=Cl, 100%)
3c: n=0, X=O (Y=Cl, 73%)



(3)

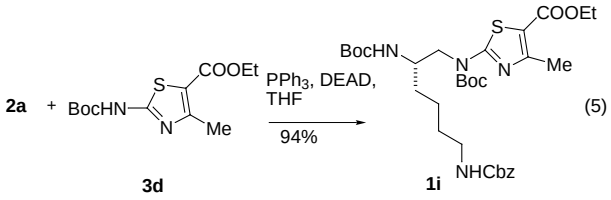
The Mitsunobu protocol[6] was utilized to prepare the reduced dipeptide isostere **1**. The desired **1a-i** were obtained from the reaction of amino alcohols **2a–d** with **3a–d** (PPh_3, DEAD or DIAD, THF, rt) in less than an hour in moderate to excellent yields after chromatographic purification[7] (Eq. 4 and 5 and Table).



(4)

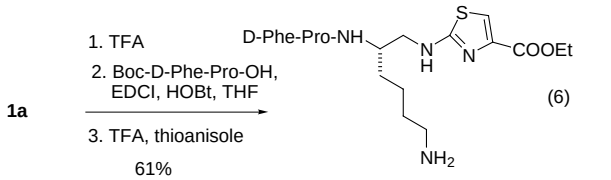
Table: Preparation of **1** from **2** and **3**.

Amino alcohol **2**:R	**3** (X,n)	Reagent	Product	Yield%
2a: CH_2NHCbz	**3a** (S, 0)	DEAD	**1a**	82
2a: CH_2NHCbz	**3b** (S,1)	DEAD	**1b**	87
2a: CH_2NHCbz	**3c** (O,0)	DIAD	**1c**	55
2a: CH_2NHCbz	**3c** (O,0)	DEAD	**1c**	45
2b: CH_2NHBoc (P=Fmoc)	**3a** (S,0)	DEAD	**1d**	83
2c: NHC(=NH)NHCbz	**3a** (S,0)	DIAD	**1e**	33
2c: NHC(=NH)NHCbz	**3c** (O,0)	DIAD	**1f**	40
2d: NHC(=NCbz)NHCbz	**3a** (S,0)	DEAD	**1g**	70
2d:NHC(=NCbz)NHCbz	**3c** (O,0)	DEAD	**1h**	40



3d **1i**

With the dipeptide isostere **1a** in hand, we synthesized tetrapeptidyl thiazole **4** based upon the sequence of the substrate D-Phe-Pro-Arg. Treatment of **1a** with TFA, followed by coupling with Boc-D-Phe-Pro-OH in the presence of EDCI/HOBt and subsequent deprotection of the Boc and Cbz groups afforded **4** in 61% yield (Eq. 6).



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In summary, we have developed a facile synthetic method for the preparation of azole bearing reduced dipeptides by the reaction of the aminoazoles with *N*-protected amino alcohols in good to excellent chemical yields.

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References and Notes

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(2) Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron Lett*. **1991**, *32*, 923.

(3) Typical Experiment of **2**:**2a**: To a stirred solution of Boc-Lys(Cbz)-OH (1.9 g, 5 mmol) in THF (10 mL) was added CDI (810 mg, 5 mmol) at r.t. After 10 min, to this stirred solution was added a solution of $NaBH_4$ (300 mg, 8 mmol) in H_2O (5 mL) in one portion at r.t. The resulting solution was then stirred at rt for 12 h. After dilution with EtOAc (100 mL), the solution was washed with 1N HCl (60 mL), sat. $NaHCO_3$ (60 mL), brine (60 mL), dried ($MgSO_4$), passed through a short pad of SiO_2, and concentrated to provide a white solid (1.94g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s and m, 15H), 3.20 (m, 2H), 3.60 (m, 3H), 4.80 (m, 2H), 5.15 (s, 2H), 7.35 (m, 5H). mp 65-68 °C (Lit.[2] 64-67 °C). The product was pure enough for the next reaction without further purification.

(4) Typical Experiment for **3**:**3a**: A mixture of ethylbromopyruvate (1.4 mL of 90% pure, 10 mmol) with thiourea (760 mg, 10 mmol) in EtOH (20 mL) was heated at reflux for 12h. Concentration gave a white solid in quantitative yield. ^{1}H NMR (500 MHz, CD_3OD) δ 1.39 (t, 3H, *J* = 7.5Hz), 4.40 (q, 2H, *J* = 7Hz), 7.71 (s, 1H). MS (ES) *m/z* 173.1 ($M+H^+$). This solid was neutralized by sat. $NaHCO_3$ and extracted with EtOAc for the use for the next reaction. To a stirred solution of above aminothiazole ester (350 mg, 2 mmol) in THF (10 mL) was added Boc_2O (440 mg, 2 mmol), followed by TEA (0.6 mL, 4 mmol) and DMAP (20 mg) at rt. After stirring at rt for 12 h, the solution was diluted with EtOAc (50 mL), washed with 1 N HCl (50 mL), dried ($MgSO_4$), passed through a short pad of SiO_2, and concentrated to provide a yellow foamy solid (460 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (t, 3H, *J* = 7Hz), 1.53 (s, 9H), 4.38 (q, 2H, *J* = 7Hz), 7.78 (s, 1H), 8.5 (br, 1H): MS (ES) *m/z* 273 ($M+H^+$).

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(7) Typical Experiment of **1**:**1a**: To a stirred solution of lysinol **2a** (39 mg, 0.1 mmol) and **3a** (27 mg, 0.1 mmol) in THF (2 mL) was added PPh_3 (40 mg, 0.15 mmol), followed by DEAD (25 μL, 0.15 mmol) at rt. After 30 min, additional PPh_3 (10 mg) and DEAD (7 μL) were added to the solution. After 30 min, the solution was concentrated to give an oil which was purified by preparative TLC (hexane: EtOAc = 80:20 to 70:30) to provide a sticky oil (51 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.34 (t, 3H, *J* = 7Hz), 1.50 (m, 6H), 1.59 (s, 9H), 3.21 (m, 2H), 4.11 (m, 3H), 4.32 (q, 2H, *J* = 7Hz), 5.07 (s and br, 3H), 7.33 (m, 5H), 7.75 (s, 1H): (CD_3OD) δ 1.24 (s, 9H), 1.37 (t, 3H, *J* = 7Hz), 1.4-1.6 (m, 6H), 1.61 (s, 9H), 3.14 (t, 2H, *J* = 7Hz), 4.0 (m, 2H), 4.25 (m, 1H), 4.36 (q, 2H, *J* = 7Hz), 5.06 (s, 2H), 6.32 (d, 1H, *J* = 9.5Hz), 7.34 (m, 5H), 7.92 (s, 1H): MS (ES) *m/z* 621 ($M+H^+$).

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