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Synthesis of Heterocyclic β-Amino Acids. A Convenient Preparation of β-Amino-5-Pyrimidinepropanoic Acid and Derivatives.

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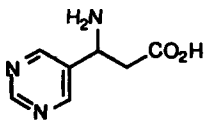
Abstract : The novel (2E)-1,1-dimethylethyl-3-(5-pyrimidinyl)-2-propenoate **3**, obtained by Heck coupling between 5-bromopyrimidine and *tert*-butyl acrylate undergoes nearly quantitative Michael addition in t-butanol saturated with ammonia to the hitherto unknown β-amino-5-pyrimidinepropanoic ester **4**. The synthetic utility of this reactions sequence is demonstrated by preparation of **4** on a multigram scale. The transformation of the ester to the free amino acid **5** and to the Cbz-N-protected amino acid **7** is described. The *tert*-butyl ester **4** and the N-protected β-amino acid **7** are useful in peptide and peptidomimic synthesis.

Beta amino acids are of considerable interest as constituents of natural products (i.e. peptides, alkaloids...)[1], as precursors for β-lactams[2] and as versatile building block for compounds with biological interest.[3] In the course of synthesizing new RGD peptidomimetics incorporating β-amino acids,[4] we needed reasonable quantities of β-amino-5-pyrimidinepropanoic acid **1**. Beta amino acids are accessible mostly through reductive amination of precursor ketones, modified Knoevenagel reaction[5] or Reformatsky reaction with Schiff bases.[6] For the present target, β-amino-5-pyrimidinepropanoic acid **1**, the properly functionalized pyrimidines required as starting materials for these classical methods are difficult to access.[7] Further complication arises from the general sensitivity of the pyrimidine ring to base. Attention was turned to a largely neglected method to access β-amino acids, the Michael addition of ammonia (or a synthetic equivalent) to acrylate derivatives.[8] The utility of this route is limited by the lack of availability of the adequate *tert*-butyl acrylate derivatives. The *tert*-butyl ester is crucial to avoid extensive formation of the primary amide, and reports on preparation of β-amino acids by this method are scarce.[9,10]



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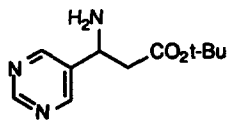

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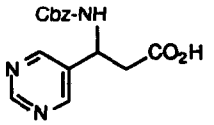

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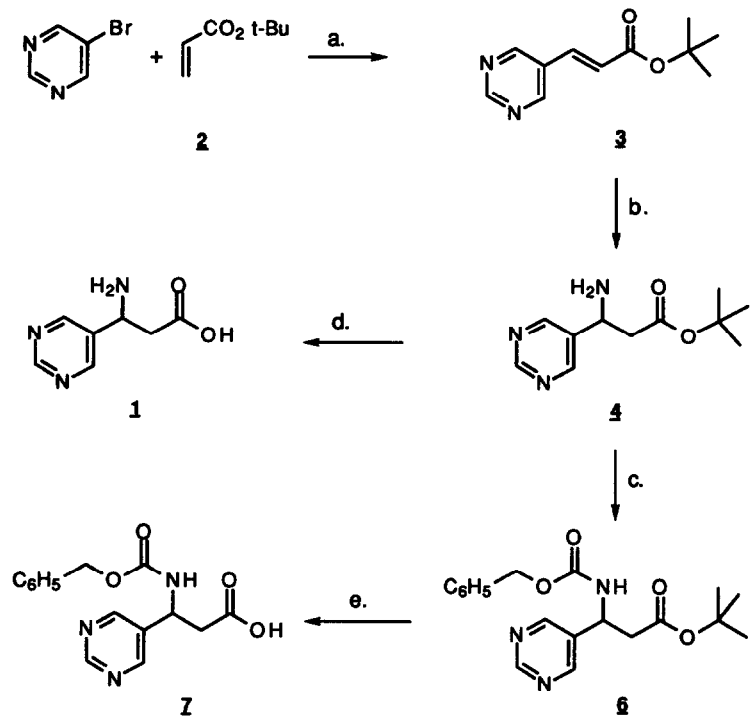
In this report, we describe an expedient synthesis of the hitherto unknown β-amino acid **1**, by the

Michael addition of ammonia to a novel *tert*-butyl acrylate derivative, 3, for which a suitable synthesis is also provided. The pyrimidine ring does not interfere, and the reaction sequence can be performed on a multigram scale. The preparation of the Cbz protected derivative 7 suitable for peptide N-terminal elongation is also described.

There are a few reports in the literature on the use of palladium-catalyzed coupling reactions[11] between halopyrimidines and olefins[12] or organometallics.[13] A palladium-catalyzed Heck coupling between 5-bromopyrimidine and *tert*-butyl acrylate was used to obtain the novel 3-(5-pyrimidinyl)-2-propenoic *tert*-butyl ester 3 (Scheme) in good yield as anticipated on the basis of the ethyl acrylate results.[14] Heating 5-bromopyrimidine at 80°C in *tert*-butyl acrylate in the presence of $Pd(OAc)_2$ and triethylamine for 72 h gave the (2E)-1,1-dimethylethyl-3-(5-pyrimidinyl)-2-propenoate 3 in 67% yield as a tan solid.[15] The use of $PdCl_2$

Scheme



a. $Pd(OAc)_2$, NEt_3, 80°C, 72 h. b.NH_3, t-BuOH, 80°C, 72 h. c. Cbz-Cl, CH_2Cl_2, N-methylmorpholine. d and e. Trifluoroacetic Acid.

resulted in a lower yield of coupling product. This compound can be used as a Michael acceptor for ammonia in alcoholic solution. It was discovered that dry ammonia in t-butanol, rather than the previously reported dry

methanol solution[18] is a superior medium for the reaction since it eliminates side reactions due to methanol transesterification and addition. The β-amino-5-pyrimidinepropanoic acid, 1,1-dimethylethyl ester **4**, was formed nearly quantitatively as indicated by ^{1}H NMR examination of the crude reaction mixture,[16] and no traces of the acrylamide **5** were observed. Reactions using solutions of ammonia in chloroform yielded no product, suggesting the need of a protic solvent. The amino ester **4** can be purified by precipitation as a salt or by chromatography. The free amino acid **1** was easily obtained by treatment with trifluoroacetic acid. The aminoester was also be reacted with benzylchloroformate to give the Cbz protected species **6** isolated as an oil. Deprotection with trifluoroacetic acid gave the N-Cbz-β-aminoacid **7** [17] which is ready for use in further peptide coupling reactions.

An expedient multigram scale synthesis of a novel substituted β-amino acid containing the base sensitive pyrimidine heterocycle has been described. The sequence that we describe makes use of a *tert*-butyl acrylate derivative, a novel precursor which allows the Michael addition to occur in high yield and provides the *tert*-butyl ester protection for the resulting amino acid carboxylic function.The preparation of the N-Cbz-protected amino acid **7** was also reported.These protected β-amino acid derivatives should have considerable utility in syntheses of new peptidomimetics. We are currently extending this reaction sequence to other sensitive β-heteroaryl amino acids.

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References and Notes

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15. (2E)-1,1-dimethylethyl-3-(5-pyrimidinyl)-2-propenoate **3**. A mixture of 5-bromopyrimidine (25 g, 0.15 mol), $Pd(OAc)_2$ (2 g, 8 mmol), 30 mL triethylamine and 300 mL *tert*-butyl acrylate was stirred at 80°C for 36 h in a pressure tube. Another load of $Pd(OAc)_2$ (2g) was added and heating resumed for another 36h. After cooling, the reaction mixture was filtered, the excess of *tert*-butyl acrylate was removed under reduced pressure and the residue crystallized from hexane as a tan solid (20 g, 67 % yield). An analytical sample recrystallized from diethyl ether melted at 117.2-117.4 °C : ^{1}H NMR (CDCl3) δ 9.2 (s, 1H), 8.8 (s, 2H), 6.8 (d, 1H, J =12.5 Hz), 6.1(d, 1H, J =12.5 Hz), 1.5 (s, 9H); FABMS (M+H) 207.1; Analysis (calcd $C_{11}H_{14}N_2O_2$, found): C 64.06, 63.83; H 6.84, 6.95; N 13.58, 13.20.
16. 1,1-dimethylethyl β-amino-5-pyrimidinepropanoate **4**. 1,1-Dimethylethyl 2-propenoate (5g) was stirred in a pressure flask with at least 10 eq. of dry ammonia in 50 mL t-butanol for 72 h at 80°C. The amino ester was isolated by precipitation from diethyl ether with HCl or by RPHPLC. The TFA salt melted at 118-119.5°C; ^{1}HNMR (DMSO) δ 1.25 (s, 9H), 2.86 (dd, 1H, J = 15Hz , J = 10 Hz), 3.1 (dd, 1H, J = 15Hz , J = 5 Hz), 4.5 (dd, 1H, J = 5 Hz, J = 10Hz). Analysis (calcd $C_{13}H_{18}N_3O_4F_3.0.5H_2O$, found) C 45.08, 45.34; H 5.38, 5.34; N 11.82, 12.15.
17. N-Cbz-β-amino-5-pyrimidinepropanoate **7**. The 1,1-dimethylethyl β-amino-5-pyrimidinepropanoate was treated with Cbz-Cl in dichloromethane and N-methylmorpholine. Aqueous work up gave the product as an oil which was stirred in trifluoroacetic acid for 3hr at 25°C. After removal of the TFA, the acid was isolated from trituration in diethyl ether (mp 141-143°C): ^{1}HNMR (DMSO) δ 2.75 (dd, 1H, J = 15 Hz, J = 6.7 Hz), 2.85 (dd, 1H, J = 15 Hz, J = 8 Hz), 5.0 (m, 3H), 7.3 (s, 5H), 8.05 (d, 1H, 8 Hz), 8.75 (s, 2H), 9.1(s, 1H); FABMS (M+H) 302.1. Analysis (calcd $C_{15}H_{15}N_3O_4$, found) C 59.79, 59.70; H 5.01, 5.02; N 13.94, 13.96.
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