A New and Practical Synthesis of α-Amino Acids from Alkenyl Boronic Acids

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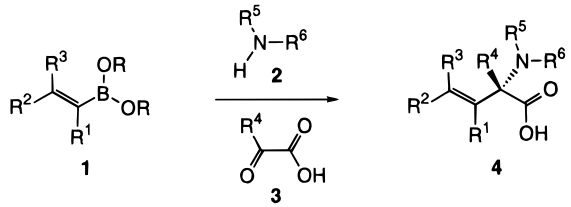
Received September 10, 1996

In recent years there has been an increasing interest for new practical methods to prepare novel non-natural α-amino acid derivatives to serve as building blocks in combinatorial chemistry and drug discovery. Although many routes to amino acids have been developed,[1] there is still a need for concise and convergent approaches that allow structure variability and facile incorporation of functional groups and ring systems.

Herein we report a new, general, and practical method[2] for the synthesis of β,γ-unsaturated α-amino acids. The parent compound in this class, vinyl glycine (**4**, $R^1-R^6 = H$), is naturally occurring[3] and has been studied extensively. Some amino acids of this type are mechanism based irreversible inhibitors[4]of various pyridoxal phosphate dependent enzymes, including amino acid aminotransferases and decarboxylases. Such compounds have previously been prepared[5] by multistep routes or by specialized methods and can serve as precursors to many other types of molecules upon further manipulation. The novel approach described herein relies on the use of organoboron compounds as the source of the side chain.[6] It is a three-component variant of the Mannich reaction[7] involving the condensation of an organoboronic acid or boronate (**1**) with an amine (**2**) and an α-keto acid (**3**).



This method extends our recently discovered process for the synthesis of geometrically pure allylamines via the condensation of amines with formaldehyde and alkenyl boronic acids.[8] A remarkable feature of this reaction is that it is triply convergent and gives products with multiple sites for introducing molecular diversity. The favorable experimental features of alkenyl boronic acids,[9] which are readily available and easy to handle crystalline compounds, have prompted us to develop new methods for their utilization in organic synthesis.[8,10] Their facile preparation from alkynes in geometrically pure form, combined with their configurational stability and their tolerance of air and water, makes these compounds highly desirable intermediates.

As shown in Table 1, alkenyl boronic acids react with amines and α-keto acids, such as glyoxylic (entries 1−10) or pyruvic acid (entry 11), to give directly the corresponding amino acids in good yields and in geometrically pure form. This reaction is practical and experimentally convenient and proceeds by the simple stirring of the three components at 25−50 °C over 12−48 h in a variety of solvents, including ethanol, toluene, and dichloromethane. Moreover, the reaction does not require anhydrous or oxygen-free conditions, and it does not utilize strong acids, strong bases, heavy metals, or other undesirable chemicals. Furthermore, since the products are usually insoluble they are easily isolated by filtration and washings with cold acetone or dichloromethane to remove unreacted starting materials and the boric acid byproduct. A simple recrystallization or ion exchange chromatography usually gives the product with high purity.

Several types of amines can participate in this process giving a variety of amino acid derivatives. These include primary amines (entries 1−9 and 11), secondary amines (entry 10), aromatic amines (entry 6), and even sterically hindered amines (entries 3 and 7). In addition to boronic acids with various substitution patterns the reaction also works with boronate derivatives (entry 9). Of special interest is the participation of bromo-substituted derivatives (**1b** and **1c**[11]) to form bromoalkenyl amino acids (entries 8 and 9). Compounds of this type were postulated to be "Trojan horse" inhibitors[4c,5m] by generating highly reactive allenic intermediates upon their exposure to the appropriate enzymes.

By using readily cleavable amines it is possible to prepare free amino acids. For example, trityl amine gives trityl-protected amino acids[12] (entry 3), which are readily deprotected under acidic conditions. Another amine that works even more efficiently for this purpose is bis(4-methoxyphenyl)methylamine[13] (entry 5). The resulting derivative (**4e**) can be readily converted to the unsubstituted amino acid (**4f**) by facile acid hydrolysis.

Asymmetric versions of this process with good to excellent stereoselectivities were observed when certain chiral amines

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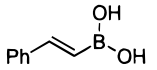
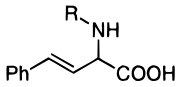
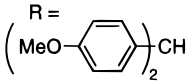
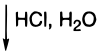
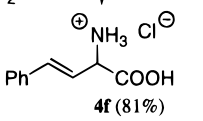
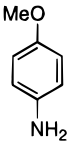
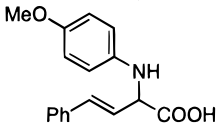
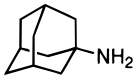
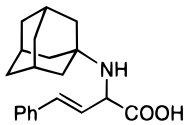
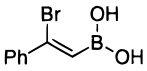
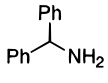
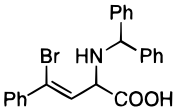
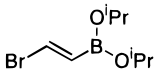
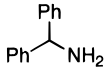
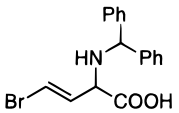
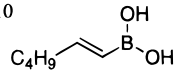
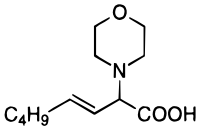
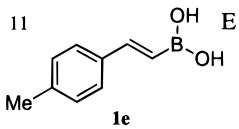
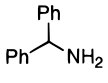
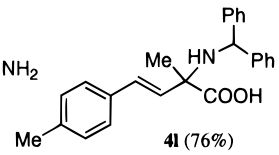
(13) Greenlee, W. J. *J. Org. Chem.* **1984**, *49*, 2632

S0002-7863(96)03178-2 CCC: $14.00

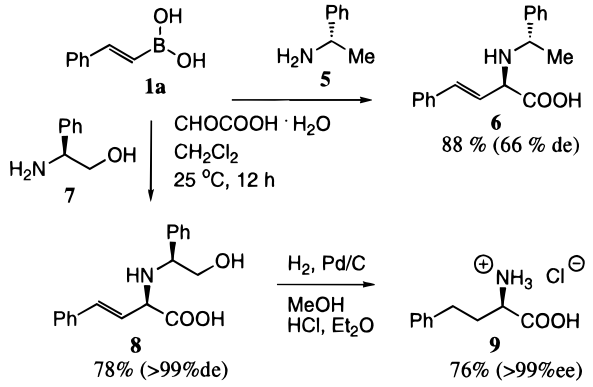
Table 1. Synthesis of Amino Acids (**4**) by the Reaction of Alkenyl Boronic Acids (**1**) with Amines (**2**) and α-Keto Acids (**3**)

	Boronic acid	Conditions[a]	Amine	Product[b] (Yield[c])
				
1	**1a**	A	R = $PhCH_2$	**4a** (87%)
2	**1a**	B	R = Ph_2CH	**4b** (94%)
3	**1a**	A	R = Ph_3C	**4c** (54%)
4	**1a**	A	R = $HOCH_2CH_2$	**4d** (82%)
5	**1a**	B	R = 	**4e** (92%)   **4f** (81%)
6	**1a**	A		 **4g** (94%)
7	**1a**	C		 **4h** (96%)
8	 **1b**	B		 **4i** (87%)
9	 **1c**	C		 **4j** (80%)
10	 **1d**	D		 **4k** (78%)
11	 **1e**	E		 **4l** (76%)

[a] A: CHOCOOH·H_2O (**3a**), EtOH, 25 °C; B: **3a**, PhMe, 25 °C; C: **3a**, CH_2Cl_2, 25 °C; D: **3a**, EtOH, 50 °C; E: MeCOCOOH (**3b**), CH_2Cl_2, 25 °C. [b] All products were geometrically pure. [c] Isolated yields after ion exchange chromatography (Dowex 50W-X8) or recrystallization from water/tert-butyl alcohol.

were used. While (*S*)-α-methylbenzylamine (**5**) gave **6** with 66% de, the use of (*S*)-2-phenylglycinol (**7**)[14] was much more effective, forming **8** in good yield and as a single diastereomer (>99% de).[15] This high degree of diastereoselectivity is quite remarkable considering that this C−C bond forming reaction was performed at room temperature! Subsequent hydrogenation of the hydrochloride salt of **8** gave (*R*)-homophenylalanine hydrochloride (**9**)[16] in enantiomerically pure form (>99% ee).[17]

Similarly, the use of (*R*)-2-phenylglycinol gave (*S*)-homophenylalanine with equal selectivity.



Although other multicomponent routes to amino acids are known, such as the Strecker[18] and Ugi syntheses,[19] these methods rely on the use of undesirable cyanide or isocyanide reagents and require more stringent experimental conditions as well as additional hydrolysis steps. The method introduced herein is more convenient and versatile in a number of ways than other reported routes. Also, while several procedures using glyoxylic acid derivatives to form electrophilic glycine equivalents have been reported,[20] the present method is shorter and milder while it provides unique ways to control the geometry and stereochemistry of the amino acid products.

Overall, this new boron-mediated reaction allows the practical, stereoselective one-pot synthesis of α-amino acids and their N-substituted derivatives. Further studies of the mechanism and scope of this process are currently underway.[21]

Acknowledgment. We gratefully acknowledge the Loker Hydrocarbon Research Institute and the donors of The Petroleum Research Fund, administered by the ACS, for partial support of this research. I.A.Z. is also grateful for a University of Southern California Merit Fellowship.

Supporting Information Available: Spectroscopic data of new compounds (8 pages). See any current masthead page for ordering and Internet access instructions.

JA963178N

(14) For a review, see: Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

(15) Experimental procedure: To a stirred solution of glyoxylic acid monohydrate (291 mg, 3.163 mmol) in CH_2Cl_2 (14 mL) was added **7** (434 mg, 3.163 mmol) in one portion, followed by **1a** (469 mg, 3.169 mmol). The reaction mixture was stirred vigorously at room temperature for 12 h. The precipitate was isolated by filtration and washed with cold CH_2Cl_2 (15 mL). The crude material gave good spectroscopic data, while ^{1}H-NMR indicated >99% de. Recrystallization from H_2O-tBuOH gave analytically pure **8** (733 mg, 78%, >99% de).

(16) Weller, H. N.; Gordon, E. M. *J. Org. Chem.* **1982**, *47*, 4160.

(17) The % ee was established by optical rotation and by ^{19}F-NMR of the Mosher amide of **9**.

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(21) We have already found that unprotected amino acids and peptides can also participate in this reaction, while asymmetric induction can also take place with chiral boronate derivatives. The reaction also works with aryl boronic acids to afford arylglycine derivatives. These results will be reported in due course.