JOC Article

Facile N-Derivatization of α-Amino Esters and Amides via Benzotriazolylmethyl Derivatives

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α-(N-Substituted amino)esters were prepared in a two-step procedure from available unsubstituted α-amino esters. α-Amino esters are first converted into the corresponding *N*-benzotriazolylmethyl derivatives; in the second step, the benzotriazole group is substituted by various nucleophiles with or without the presence of a Lewis acid to give substituted α-amino esters in high overall yield under mild conditions with no signs of racemization. Boc-protected amino acids were converted into α-amino amides; subsequent deprotection allowed the conversion into N-substituted derivatives analogously to the α-amino esters, without racemization in high yields under mild conditions.

Introduction

N-Substituted amino esters and amides have been extensively investigated and heavily patented for pharmacological applications as antiinflammatory,[1] antiischemic,[2] antineoplastic,[3] antiallergic,[4] and antidiabetic[5] agents.

Commonly, reductive amination[6] and direct N-alkylation[7] have been used to provide N-alkylated amino esters and amides. N-Monoalkylation of α-amino esters with alkyl halides as reported by Jung advantageously employs cerium hydroxide;[8] Kim et al.[9] found that, of a variety of alkali and alkali earth metal hydroxides and carbonates, only lithium hydroxide gave N-alkylated products in good yields.

Derivatizations of amino functionality via conversion into *N*-benzotriazolylmethyl derivatives followed by reactions with a variety of nucleophiles in the presence of a Lewis acid are well-known.[10] This protocol was previously applied to the functionalization of chiral N-substituted 4-phenyloxazolidine-2-carboxylates[11a] and L-proline and pipecolinic esters.[11b] *N*-(Benzotriazolylmethyl)phenylalanine derivatives were stereoselectively cyclized into 1,2,3,4-tetrahydroisoquinoline-3-carboxylates under mild conditions.[12] We now report an efficient protocol for the derivatization of α-amino esters and amides via nucleophilic substitution of the corresponding benzotriazolylmethyl derivatives.

Results and Discussion

Preparation of N-Functionalized α-Amino Esters (3a−j). *N*-Benzotriazolylmethyl α-amino esters (**2a−c**) were prepared in yields of about 70−90% using a standard procedure[12] from the respective amino ester, benzotriazole, and aqueous formaldehyde at ambient temperature (Scheme 1). Solid product **2a** was easily purified by recrystallization from chloroform/hexanes. Products **2b**,**c**, obtained as oils, were labile on silica gel and were used directly for subsequent reactions without further purification.

Compounds **2a−c**, in the presence of Lewis acids, form iminium ions that are prone to nucleophilic attack and react with different types of nucleophiles in the presence or absence of appropriate Lewis acids. A boron fluoride etherate complex was used as a catalyst in reactions of *N*-(benzotriazolylmethyl)amino esters **2a**,**b** with allyltrimethylsilane (Table 1, entries 3 and 6). In reactions performed at 0 °C for 2 h and at room temperature for 12 h, **3c** and **3f** were obtained in 68 and 42% yield,

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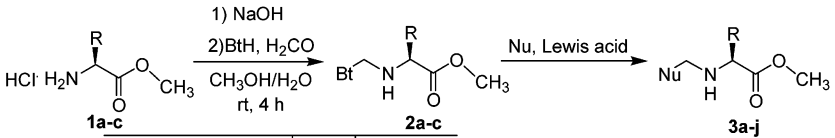
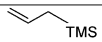
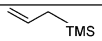
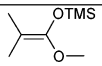
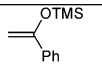
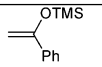
SCHEME 1



Compounds **1** and **2**	R	Yield of **2**
a	Bn	81*
b	Ph	70**
c	Me	75**

* - isolated yield
**-yield according to a crude NMR

TABLE 1. Preparation of N-Functionalized α-Amino Esters 3a−j

Entry	Product	R	Nucleophile	Lewis Acid	Nu in **3**	Yield of **3**, %[a]
1	**3a**	Bn	PhSH/NaH	N/R[b]	SPh	85
2	**3b**	Bn	$P(OEt)_3$	$ZnBr_2$	$PO(OEt)_2$	62
3	**3c**	Bn		$BF_3.Et_2O$	allyl	68
4	**3d**	Bn		$BF_3.Et_2O$	$C(CH_3)_2CO_2CH_3$	75
5	**3e**	Bn	NaCN	N/R[b]	CN	98
6	**3f**	Ph		$BF_3.Et_2O$	allyl	42[c]
7	**3g**	Ph		$BF_3.Et_2O$	$C(CH_3)_2CO_2CH_3$	51[c]
8	**3h**	Ph		$BF_3.Et_2O$	CH_2COPh	40[c]
9	**3i**	Ph	NaCN	N/R[b]	CN	62[c]
10	**3j**	Me		$BF_3.Et_2O$	CH_2COPh	55[c]

[a] Isolated yields, except of **3a**. [b] Not required. [c] Yield of compound is calculated for two steps and based on **1b**,**c**.

respectively, after purification by column chromatography on silica. Silylenol ethers were used in similar transformations for the preparation of ester derivatives **3d**,**g** (Table 1, entries 4 and 7) and alkyl phenyl ketones **3h**,**j** (Table 1, entries 8 and 10). Compounds **3d**,**g**,**h**,**j** were obtained in 40−75% yields after purification on silica.

Reaction of **2a** with triethyl phosphite requires $ZnBr_2$ as a catalyst (Table 1, Entry 2). Triethyl phosphite was used in 2-fold excess. The reaction was performed at 0 °C for 1 h and at room temperature for 14 h. Compound **3b** was obtained in 62% yield after the purification on silica. Characteristic couplings of protons to phosphorus were observed in ^{1}H NMR spectra. Ethyl groups and $P-CH_2-N$ were observed as multiplets. Carbon couplings of 158.6, 15.5, and 5.7 Hz to phosphorus were observed in the ^{13}C NMR spectrum and are in the usual range for such compounds.

The nucleophiles CN^- or ArS^- do not require the use of Lewis acids. Compound **3a** (Nu = PhS) was formed in 85% yield according to ^{1}H NMR data of the crude reaction mixture. However, attempts to purify this compound by chromatography on silica or aluminum oxide or recrystallization failed due to the low stability of the final compound **3a**.

The benzotriazolyl group was easily substituted by a cyano anion to afford **3e** and **3i** in 98% and 62% yields, respectively (Table 1, entries 5 and 9). The reaction was carried out in DMSO at room temperature for 48 h. Compound **3e** was obtained as a pure product without additional purification. Compound **3i** was purified by flash column chromatography on silica in order to remove the admixture of DMSO.

Preparation of N-Functionalized α-Amino Amides (8a−f). Starting α-amino amides **6a−c** were obtained according to a previously published protocol starting from *N*-Boc-protected α-amino acids[12,13] (Scheme 2). Amino acids **4a−c** were converted into the corresponding amides **5a−c** which underwent a standard deprotection with 20% solution of TFA in dichloromethane to form compounds **6a−c**.

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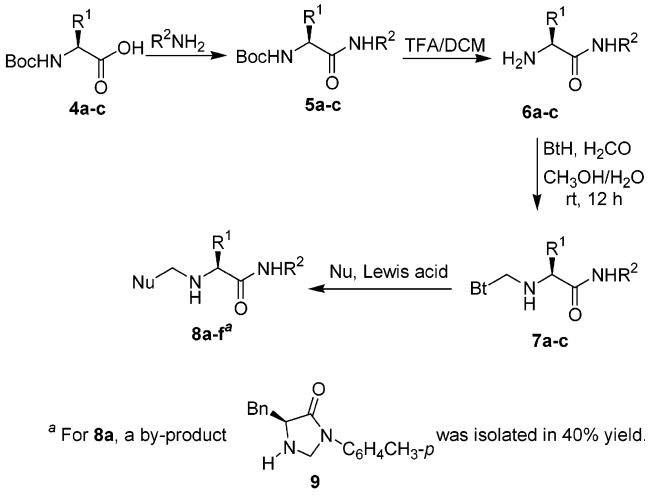
SCHEME 2



SCHEME 3

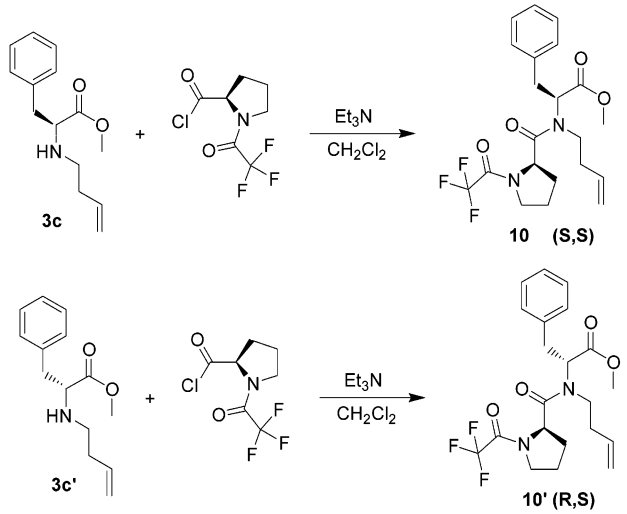


TABLE 2. Preparation of *N*-Benzotriazolylmethyl-α-amino Amides 7a−c

entry	**7a−c**	R^1	R^2	yield of **7**, %
1	**7a**	Bn	4-$CH_3C_6H_4$−	80
2	**7b**	Me	Bn	93
3	**7c**	*i*-Bu	4-$CH_3C_6H_4$−	86

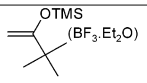
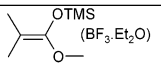
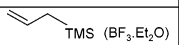
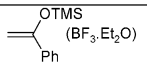
Compounds **6a−c** were reacted with benzotriazole and aqueous formaldehyde in methanol/water mixture for 12 h at room temperature to give *N*-benzotriazolylmethyl-α-amino amides **7a−c** (Scheme 2, Table 2). Compounds **7a−c** were obtained as benzotriazole-1-yl isomers with traces of benzotriazole-2-yl derivatives. Purification of compounds **7a−c** by recrystallization gave pure benzotriazole-1-yl derivatives in 80−93% yield (Table 2). Two doublets and two triplets in the 7.20−8.20 ppm region in ^{1}H NMR spectra correspond to the benzotriazole-1-yl moiety and support the structural assignments of **7a−c**.

Compounds **7a−c** were reacted with different nucleophiles in the presence or absence of appropriate Lewis acids (Scheme 2, Table 3). All reactions were performed under standard general conditions: stirring at 0 °C for 2 h followed by stirring at room temperature for 16 h. In all cases, a BF_3·Et_2O complex was used as a nucleophilic substitution catalyst of benzotriazole moiety. Final compounds **8c−e** were obtained in 61−82% yields after purification by column chromatography. In the case of the reaction of **7a** with (2,2-dimethyl-1-methylenepropoxy)trimethylsilane, compound **8a** was obtained in 50% yield along with product **9** as a result of the concurrent intramolecular substitution of benzotriazole by the amide nitrogen. Compound **9** was isolated in 40% yield.

The use of sodium cyanide as a nucleophile does not require the presence of Lewis acid. Compounds **8b** and **8f** were obtained in 89 and 92% yield with analytical purity and did not require additional purification.

In our first attempt to estimate the enantiomeric purity of the final compounds, we prepared each of the enantiomers **3c** and **3c′** from enantio pure L- and D-phenylalanine, respectively. However, analysis of individual and mixed samples of **3c** and **3c′** by HPLC using a chiral column showed a very small difference in retention time for enatiomers and no distinct separation of **3c** and **3c′** was possible under the condition used. Therefore, we reacted each of the enantiomers **3c** and **3c′** with (*S*)-(−)-trifluoroacetyl prolyl chloride (Scheme 3) and ana-

TABLE 3. Preparation of N-Functionalized α-Amino Amides 8a−f

Entry	**8**	R^1	R^2	Nucleophile	Nu	Yield of **8**, %
1	**a**	Bn	4-$CH_3C_6H_4$-		$CH_2COC(CH_3)_3$	50[a]
2	**b**	Bn	4-$CH_3C_6H_4$-	NaCN	CN	92
3	**c**	Me	Bn		$C(CH_3)_2CO_2CH_3$	82
4	**d**	Me	Bn		allyl	61
5	**e**	*i*-Bu	4-$CH_3C_6H_4$-		CH_2COPh	64
6	**f**	*i*-Bu	4-$CH_3C_6H_4$-	NaCN	CN	89

[a] By-product of intramolecular cyclization **9a** was obtained in 40% yield (Scheme 2). In all other reactions, the intramolecular cyclization was not observed.

lyzed the compounds **10** and **10′** thus obtained by TLC and by ^{1}H, ^{13}C, and ^{19}F NMR. The chemical shift in the ^{19}F NMR spectrum (Figure 11, Supporting Information) for compound **10** is at −72.907, for **10′** (Figure 12, Supporting Information) at −73.069. The analysis of mixed sample clearly showed the difference in chemical shifts (Figure 13, Supporting Information). In compound **10′**, the presence of about 5% of **10** was detected; this is in accordance with the enantiomeric purity of the starting D-phenylalanine (Figure 12, Supporting Information). TLC analysis of individual diastereomers and a mixed sample also clearly showed the difference between diastereomers **10** and **10′**. All other products were assigned by analogy and by comparison of their ^{1}H and ^{13}C NMR spectra.

Conclusions

In this paper, we disclose an efficient method for the preparation of N-functionalized α-amino esters and amides. Whereas previous investigations on functionalization of chiral α-amino esters were limited to N-substituted 4-phenyloxazolidine-2-carboxylates and L-proline and pipecolinic esters[11] which represent cyclic secondary amino function, the present results are now extended to noncyclic α-amino esters and α-amino amides. The described protocol utilizes mild conditions and provides high yields of final compounds **3a**−**j**, **8a**−**f** and intermediates **2a**−**c**, **7a**−**c**.

Experimental Section

Melting points were determined using a capillary melting point apparatus equipped with a digital thermometer and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a 300 NMR spectrometer in $CDCl_3$ (with TMS for ^{1}H and chloroform-*d* for ^{13}C as the internal reference). Optical rotation values were measured with the use of the sodium D line. Column chromatography was performed on silica gel (200−425 mesh) unless otherwise stated. All of the reactions were carried out under N_2. The HPLC system consisted of a isocratic pump, variable-wavelength UV/vis detector, and a computing integrator. Injector is fitted with a 20-μL loop and detection was performed at 254 nm. A 25 cm × 4.6 mm LC-(R)-DNB-PG column was used for the chiral separation with hexane (99.8%)/*i*-PrOH(0.2%) at 1.5 mL/min flow rate as an eluent.

General Procedure for the Preparation of *N*-Benzotriazolylmethyl α-amino Esters 2a−c. To a solution of benzotriazole (11.0 mmol) and the hydrochloric salt of **1a**−**c** (10.0 mmol) and NaOH (10.0 mmol) in MeOH/H_2O (20/10 mL) was added formaldehyde (10.0 mmol, 37% aqueous solution). The mixture was stirred at room temperature for 4 h. For **2a**, the obtained precipitate was filtered, washed with cold H_2O and EtOH, and recrystallized from $CHCl_3$/hexanes. For **2b**,**c**, the products were extracted with diethyl ether. The organic extracts were dried over $MgSO_4$, and the solvent was removed to dryness under reduced pressure to give crude compounds **2b**−**c**, which were used in the next step without purification.

Reaction of 2a with Thiophenol. To a solution of thiophenol (0.31 mL, 3.0 mmol) in dry THF (20 mL) was added NaH (60% in mineral oil, 0.16 g, 4.0 mmol), and the reaction mixture was stirred at 20−25 °C for 1 h. One drop of methanol was added to quench excess NaH, and then methyl (2*S*)-2-[(1*H*-benzotriazol-1-ylmethyl)amino]-3-phenylpropanoate **2a** (0.62 g, 2.0 mmol) was added. The mixture was stirred at 25 °C for 24 h. After removal of THF in vacuo, 10% aqueous Na_2CO_3 was added to the residue, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded the desired product **3a**.

Reaction of 2a with Triethyl Phosphite. To a solution of **2a** (0.62 g, 2.0 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C were sequentially added $ZnBr_2$ (0.90 g, 4.0 mmol) and triethyl phosphite (0.69 mL, 4.0 mmol). The reaction mixture was stirred at 0 °C for 1 h and at 25 °C for 14 h. The reaction mixture was quenched with a 10% solution of Na_2CO_3 and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by gradient column chromatography (silica gel) with EtOAc/hexanes (5% of EtOAc to 50% of EtOAc, 5% step) as eluent to afford **3b**.

General Procedure for the Reaction of 2a,b with NaCN. A mixture of **2a**,**b** (2.0 mmol) and NaCN (2.7 mmol) in DMSO (10 mL) was stirred at 20−25 °C for 48 h. The solution was diluted with EtOAc (20−25 mL), washed with water, 5% Na_2CO_3, and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, **3e** was obtained as a pure compound without additional purification; compound **3i** was purified by gradient silica gel column chromatography with EtOAc/hexanes (5% of EtOAc to 50% of EtOAc, step 5%) as eluent. Compound **3e** has been published previously.[14]

General Procedure for the Reaction of 2a−c with Allyl Silanes and Silylenol Ethers. N-Functionalized α-amino esters **2** (2.0 mmol) and allylsilanes (3 mmol) or silyl enol ethers (3 mmol) were dissolved in dry dichloromethane (12 mL). The solution was cooled to 0 °C using an ice bath, and $BF_3{\cdot}Et_2O$ (3.0 mmol) was added. The mixture was allowed to react at 0 °C for 2 h and at 25 °C for 12 h. The reaction mixture was quenched with a 10% aqueous solution of Na_2CO_3 and extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by gradient column chromatography (silica gel) with EtOAc/hexanes (5% of EtOAc to 50% of EtOAc, 5% step) to afford **3c**,**d**,**f**−**h**,**j**. Compounds **3g**,**j** have been published previously.[15,16]

General Procedure for the Preparation of *N*-Benzotriazolylmethyl α-Amino Amides 7a−c. A mixture of **6** (3.0 mmol), benzotriazole (3.0 mmol), and formaldehyde (37% aqueous solution, 3.0 mmol) in CH_3OH/H_2O (6 mL/3 mL) was stirred at 25 °C for 12 h. The precipitate was filtered, washed with cold diethyl ether, and recrystallized from appropriate solvents to give **7a**−**c**.

General Procedure for the Reaction of 7a−c with Allyl Silanes and Silylenol Ethers. *N*-Benzotriazolylmethyl α-amino amides **7a**−**c** (1.0 mmol) and allyl silanes (1.5 mmol) or silylenol ethers (1.5 mmol) were dissolved in dry CH_2Cl_2 (7 mL). The solution was cooled to 0 °C using an ice bath, and $BF_3{\cdot}Et_2O$ (1.5 mmol) was added. The mixture was allowed to react at 0 °C for 2 h and at 25 °C for 16 h. The reaction mixture was quenched with a 10% solution of Na_2CO_3 and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by gradient column chromatography (silica gel) with EtOAc/hexanes (5% of EtOAc to 50% of EtOAc, 5% step) to afford **8a** and **9a**, **8c**−**e**.

Reaction of 7a and 7c with NaCN. A mixture of **7a** or **7c** (1.0 mmol) and NaCN (1.3 mmol) were dissolved in DMSO (7 mL) and stirred at 20−25 °C for 14 h. The solution was diluted with EtOAc, washed with water and 5% Na_2CO_3, and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by silica gel column chromatography with EtOAc/hexanes (1/2) as eluent to afford **8b**,**f**.

Preparation of Compounds 10 and 10′. Respective compound **3c**, **3c′** (0.03 g, 0.13 mmol) and triethylamine (0.02 mL, 0.13 mmol) were added to the solution of (*S*)-(−)-(trifluoroacetyl)prolyl chloride (1.3 mL, 0.13 mmol, 0.1 M solution in DCM) at 0 °C, and the reaction mixture was stirred at room temperature for 12 h. After addition of water, the mixture was

extracted with EtOAc and washed with 10% HCl. The combined organic layers were dried over anhydrous sodium sulfate and evaporated to dryness to give compounds **10**, **10′**. Additionally, compounds **10**, **10′** can be purified by column chromatography with ethyl acetate/hexanes from 1/5 to 1/3.

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Supporting Information Available: Descriptions of NMR data, CHN, or HRMS and physical properties for all compounds, copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **3a**,**b** and **8d**−**f**, ^{19}F NMR spectra for individual compounds **10** and **10′**, ^{19}F NMR spectrum for the mixture of **10** and **10′**, and TLC for **10** and **10′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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