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Amino Acyl Conjugates of Nitrogen Heterocycles as Potential Pharmacophores

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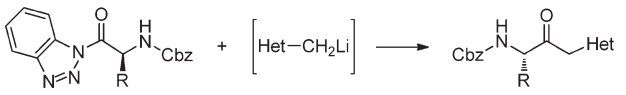


2-Methyl- and 4-methylpyridine and 2-methylquinoline are converted by benzotriazole-activated (Cbz)-protected amino acids into chiral potential novel pharmacophore aminoacyl conjugates (33−53%).

α-Amino acids and their derivatives are central to the chemistry and biology of peptides and proteins as well as versatile synthetic building blocks for pharmaceutical applications, precursors for the generation of molecular diversity, important templates in asymmetric catalysis, and common subunits in many bioactive compounds and natural products.[1]

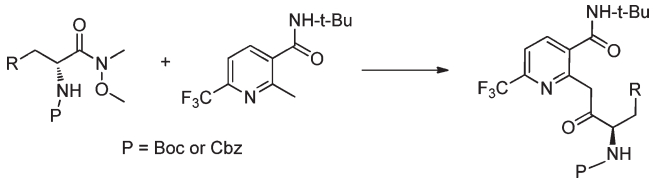
Pyridine and quinoline scaffolds possess important pharmacological activities including anti-inflammatory,[2,3] anticonvulsant,[4,5] antibacterial,[6,7] antihistaminic,[8] and anticancer.[9] Pyridines substituted by α-aminoacyl groups include useful drugs for osteoporosis and other metabolic bone diseases,[10,11] potent inhibitors of nitric oxide synthase (NOS) isozymes,[12] effective biochemical markers of bone resorption,[13] efficient organogelators,[14] and bacterial growth inhibitors.[15]

Amino acids and peptides attached to a drug scaffold can increase solubility, selectivity, and bioavailability; thus, the biological activity of 6,11-dimethyl-6*H*-indolo[2,3-*b*]quinoline is increased in amino acid derivatives.[16] The antitumor activity of *N*-L-leucine-doxorubicin shows increased selectivity over doxorubicin (Dox).[17]

N-Acylbenzotriazoles are advantageous for (i) *N*-acylation in the preparation of primary, secondary, tertiary,[18] and heterocyclic amides,[19] Weinreb amides,[20] and *N*- acylindoles,[17] (ii) *C*-acylation in the preparation of β-ketosulfones,[21] primary and secondary α-cyanonitriles,[22] α-nitroketones,[23] ketones,[24] and α-ketoazines,[25] and (iii) *O*-acylation of aldehydes[26] and of steroids[27] to give esters.

C-Acylation[28,29] of 2-methylnicotinamides has previously been achieved using Weinreb amides in the presence of LDA/TMEDA and *i*-PrMgCl/THF (Scheme 1, 70%)[29] and coupling reagents such as HOBt, but the procedures lead to racemization under a variety of conditions.[29]

SCHEME 1



We now report a convenient one-step conversion of 2-methyl- and 4-methylpyridine and 2-methylquinoline into protected amino acyl conjugates as potential model pharamacophores; a single analogous example was published

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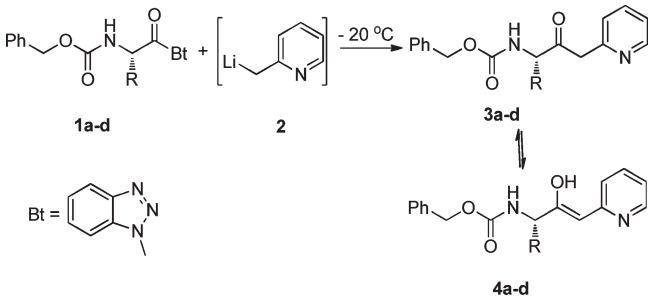
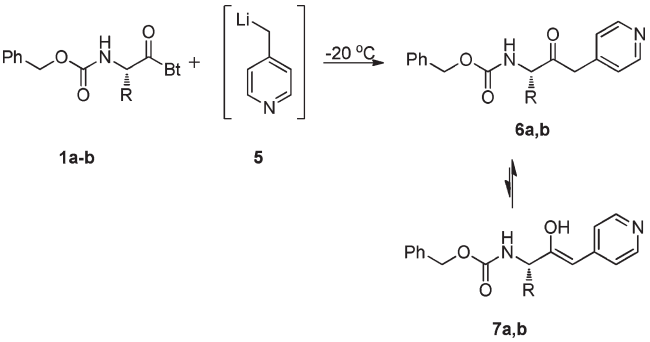
TABLE 1. Preparation of *N*-Cbz-Protected (α-Aminoacyl)methylenepyridines and -quinolines

reactant	Het-CH_3	product	% keto form	yield (%)	$[\alpha]^{25}_D$
Z-L-Ala-Bt **1a**	2-methylpyridine	Z-Ala-CH_2-2-(pyridyl) (**3a** + **4a**)	71	50	+7.57
Z-L-Val-Bt **1b**	2-methylpyridine	Z-Val-CH_2-2-(pyridyl) (**3b** + **4b**)	59	50	+2.00
Z-L-Ile-Bt **1c**	2-methylpyridine	Z-Ile-CH_2-2-(pyridyl) (**3c** + **4c**)	59	53	−11.03
Z-L-Trp-Bt **1d**	2-methylpyridine	Z-Trp-CH_2-2-(pyridyl) (**3d** + **4d**)	67	33	+26.25
Z-L-Ala-Bt **1a**	4-methylpyridine	Z-Ala-CH_2-4-(pyridyl) **6a**	100	44	−5.00
Z-L-Val-Bt **1b**	4-methylpyridine	Z-Val-CH_2-4-(pyridyl) **6b**	100	46	+19.25
Z-L-Ala-Bt **1a**	2-methylquinoline	Z-Ala-CH_2-2-(quinolinyl) **9a**	0	48	−25.5
$Z-_{DL}$-Ala-Bt (**1a** + **1a′**)	2-methylquinoline	Z-Ala-CH_2-2-(quinolinyl) (**9a** + **9a′**)	0	32	Racemic
Z-L-Val-Bt **1b**	2-methylquinoline	Z-Val-CH_2-2- (quinolinyl) **9b**	0	53	−79.8
Z-L-Ile-Bt **1c**	2-methylquinoline	Z-Ile-CH_2-2-(quinolinyl) **9c**	0	52	−70.26
Z-L-Trp-Bt **1d**	2-methylquinoline	Z-Trp-CH_2-2-(quinolinyl) **9d**	0	49	+6.63
Z-L-Lys(Z)-Bt **1e**	2-methylquinoline	Z-Lys(Z)-CH_2-2-(quinolinyl) **9e**	0	52	−39.3

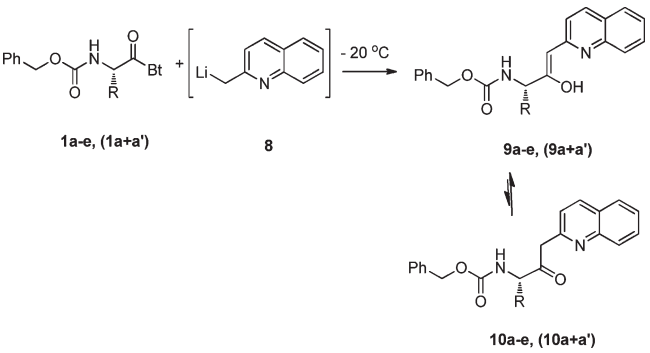
SCHEME 2



SCHEME 3



SCHEME 4



previously with optical rotation as the only measurement of chirality.[30]

Lithiation of 2-methylpyridine using *n*-BuLi in dry THF−hexamethylphosphoramide (HMPA) at −78 °C followed by reaction of **2** with *N*-Cbz-α-aminoacylbenzotriazoles[31] (**1a**−**d**) gave 2-(*N*-Cbz-α-aminoacyl)methylpyridines (**3a**−**d** and **4a**−**d**) (33−53%) (Scheme 2, Table 1).

In $CDCl_3$ solution, these compounds exist as mixtures of keto **3a**−**d** and enol **4a**−**d** tautomers as demonstrated by their ^1H and ^{13}C NMR spectra. The ratios of the keto and enolic forms (given in Table 1) are calculated from ^1H NMR integrals. The ^1H NMR spectrum of (**3a** + **4a**) showed an enolic methine proton singlet at δ 5.17 and a characteristic AB quartet for the α-methylene carbon of the keto form at δ 4.10 and 4.00. The ^{13}C NMR spectrum of (**3a**+**4a**) showed the enolic methine carbon signal at δ 91.8 and that for the α-methylene carbon of the keto form at δ 48.5.

Similarly, lithiation of 4-methylpyridine using LDA at −78 °C in dry THF and treatment with *N*-Cbz-protected (α-aminoacyl)benzotriazoles (**1a**,**b**) gave *N*-(α-Cbz-aminoacyl)methylene heterocycles (**6a**,**b**) (44−46%) (Scheme 3, Table 1). Compounds **6a**,**b** exist essentially completely in the keto forms (**6a**,**b**). Thus, the ^1H NMR spectrum of **6a** showed the α-methylene proton of the keto form as a singlet at δ 3.80. The ^{13}C NMR spectrum showed signals for the carbonyl group and for the α-methylene carbon of the keto form at δ 204.9 and 44.9, respectively. No enolic OH signal was found.

Again, treatment of *N*-(Cbz-α-aminoacyl)benzotriazoles (**1a**−**e**, (**1a** + **1a′**)) with lithiated 2-methylquinoline (**8**) gave *N*-Cbz-protected (α-aminoacyl)methylene heterocycles (**9a**−**e**, (**9a** + **9a′**)) in 32−53% yield. (Scheme 4, Table 1) These compounds exist in $CDCl_3$ solution essentially completely in their enolic forms (**9a**−**e**, (**9a**+**9a′**)). Thus, the ^1H NMR spectrum of **9a** showed a methine proton singlet at δ 5.37 and the **9a** ^{13}C NMR spectrum showed the δ 88.9 signal characteristic of an enolic methine carbon. No quinolin-2-CH_2 group signal was found.

As discussed above, the compounds derived from 2-picoline exist in $CDCl_3$ solution as mixture of the keto **3a**−**d** (58−70%) and enol **4a**−**d** (30−42%) tautomers. The compounds derived from 2-methylquinoline exist essentially in the enolic form **9a**−**e** or (**9a** + **9a′**), which are stabilized by intramolecular H-bonds from the enolic OH group with the nitrogen of the heterocycle. By contrast, compound **6a** and **6b** (derived from 4-picoline) where these could be no intramolecular H-bonding in the enols, exist essentially completely as keto forms.

The chiral integrity of compound **9a** was established by normal-phase hexane/2-propanol chromatography on a

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TABLE 2. Synthesis of N-Protected (α-Aminoacyl)benzotriazoles 1a−e, 1a′

products (**1**)	mp (°C)	lit. mp (°C)	$[\alpha]^{25}_D$
Z-L-Ala-Bt (**1a**)	114−115.5	114.0−115.0	−8.0
Z-DL-Ala-Bt (**1a** + **1a′**)	111.0−112.0	112.0−113.0	racemic
Z-L-Val-Bt (**1b**)	106.8−108.3	73.0−74.0	−30.5
Z-L-Ile -Bt (**1c**)	77.5−78.8	73.0−75.0	−3.93
Z-L-Trp-Bt (**1d**)	104.0−105.0	100.0−101.0	+25.27
Z-L-Lys(Z)-Bt (**1e**)	74.0−83.0	novel	−24.50

Chiralcel OD-H column with (+) ESI-MS: **9a** showed one major peak (retention time 34.4 min). By contrast, racemic mixture (**9a** + **9a′**) revealed two peaks with retention times of 34.4 and 61.4 min but each of mass 348. Clearly, the peak at 34.4 min is the L-isomer **9a** and the peak at 61.4 min is the D-isomer **9a′**. Compound **9a** and racemic mixture (**9a** + **9a′**) were also analyzed via reversed-phase gradient nonchiral C-18 HPLC-MS. Each displayed only one major peak (MW 348), eluting at essentially the same retention time (40.34 and 40.22 min, respectively).

In conclusion, we have described a general and convenient one-step preparation of chirally pure aminoacyl conjugates of pyridine and quinoline (33−53%) with simple preparative and purification procedures. The literature method[29] for the preparation of these bioactive compounds involved several steps and a coupling reagent (HOBt on *i*-PrMgCl) and led to racemization, speculated to result from H-bonding between the pyridine nitrogen and enolic OH group.[29] In contrast, our synthesized example **9a** (alanine−quinoline conjugate), which exists essentially in the enolic form, is chirally pure.

The advantages of using Bt-activation include: (a) good yields, (b) simple preparative and purification procedures, (c) applicability to a variety of carbobenzyloxy (Cbz)-protected amino acids, and (d) low cost.

Experimental Section

General Procedure for the Preparation of *N*-Cbz-protected (α-Aminoacyl)benzotriazoles 1a−e. Compounds are synthesized following our established procedure (Tables 2).[31]

(*S*)-Benzyl 6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-6-oxohexane-1,5-diyldicarbamate (Z-Lys(*Z*)-Bt) (1e): white-tan powder; mp 74.0−83.0 °C (50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 8.1 Hz, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.31 (br s, 9H), 7.11 (br s, 1H), 5.92−5.86 (br s, 1H), 5.82−5.72 (m, 1H), 5.13−5.08 (m, 2H), 5.08−5.02 (m, 2H), 4.92 (br s, 1H), 3.29−3.06 (m, 2H), 2.20−2.02 (m, 1H), 1.99−1.82 (m, 1H), 1.66−1.42 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 156.8, 156.3, 146.1, 136.7, 136.2, 131.2, 130.8, 128.6, 128.3, 128.1, 126.6, 120.5, 114.5, 67.4, 66.8, 54.6, 40.3, 32.4, 29.4, 22.6. Anal. Calcd for $C_{28}H_{29}N_5O_5$: C, 65.23; H, 5.67; N, 13.58. Found: C, 65.37; H, 6.04; N, 13.33.

General Procedure for the Preparation of *N*-Cbz-protected (α-Aminoacyl)methylene Heterocycles 3a−d, 4a−d, 9a−e, and 9a′. A solution of *n*-BuLi (2.5 equiv, 1.6 M in hexane) and HMPA (6 equiv) was added dropwise to a solution of **2** or **6** (1 equiv) in dry THF (30 mL) at −78 °C, and the mixture was stirred for 3 h. The temperature was then allowed to rise to −20 °C, and a solution of *N*-Cbz-α-aminoacyl-Bt (1 equiv) in dry THF (20 mL) was added by syringe at −20 °C under nitrogen. The resulting mixture was stirred at −20 °C for 1−3 h, quenched with water (20 mL), and extracted with ethyl acetate (150 mL). The organic layer was washed with saturated sodium carbonate solution (1 M, 3 × 50 mL) and dried over anhydrous magnesium sulfate and solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluent to give the expected product.

(*S*)-Benzyl 3-oxo-4-(pyridin-2-yl)butan-2-ylcarbamate (3a + 4a): yellow oil (50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (keto form **3a**) 8.53 (d, J = 3.6 Hz, 1H), 7.66 (t, J = 7.2 Hz, 1H), 7.42−7.28 (m, 5H), 7.30−7.16 (m, 2H), 5.84−5.77 (m, 1H), 5.17−5.06 (m, 2H), 4.58−4.47 (m, 1H), 4.08 (d, J = 15.6 Hz, 1H, A part of AB system), 4.00 (d, J = 15.9 Hz, 1H, B part of AB system), 1.40 (d, J = 6.9 Hz, 3H), (enol form **4a**) 8.03 (d, J = 5.4 Hz, 0.4H), 7.53 (t, J = 6.8 Hz, 0.8H), 7.42−7.28 (m, 2.0H), 6.92−6.83 (m, 0.8H), 5.42 (s, 0.4H), 5.17−5.06 (m, 0.8H), 5.02−4.98 (m,0.4H), 4.44−4.32 (m, 0.4H), 1.40 (d, J = 6.9 Hz, 1.2H); ^{13}C NMR (75 MHz, $CDCl_3$) keto + enol form (**3a** + **4a**) δ 205.8, 155.7, 154.2, 149.5, 141.5, 137.4, 136.8, 136.3, 128.5, 128.1, 128.0, 124.2, 122.2, 121.2, 117.0, 91.8, 66.9, 55.7, 51.4, 48.5, 20.1, 17.6. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.08; H, 6.50; N, 9.20.

(*S,Z*)-Benzyl 3-hydroxy-4-(quinolin-2-yl)but-3-en-2-ylcarbamate 9a: yellow crystals; mp 56.4 °C (48%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.69 (s, 1H), 7.59 (d, J = 9.3 Hz, 1H), 7.50 (t, J = 7.4 Hz, 2H), 7.41−7.28 (m, 6H), 7.28−7.18 (m, 1H), 6.70 (d, J = 9.0 Hz, 1H), 5.72 (d, J = 6.3 Hz, 1H), 5.37 (s, 1H), 5.20−5.04 (m, 2H), 4.48−4.34 (m, 1H), 1.41 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.6, 155.7, 153.5, 136.9, 136.7, 136.4, 131.1, 128.4, 128.0, 127.9, 127.6, 123.6, 122.8, 121.9, 117.1, 88.9, 66.5, 53.5, 20.3. Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.79; N, 8.04. Found: C, 72.16; H, 5.45; N, 8.05.

General Procedure for the Preparation of *N*-Cbz-protected (α-Aminoacyl)methylene Heterocycles 6a,b. To 4-picoline (1 equiv) in dry THF (30 mL) was added LDA (2.0 equiv) dropwise during 15 min at −78 °C and the mixture stirred for 3 h. The temperature was then allowed to rise to −20 °C, and a solution of *N*-Cbz-α-aminoacyl-Bt (1 equiv) in dry THF (20 mL) was added by syringe at −20 °C under nitrogen. The resulting mixture was stirred at −20 °C for 1 h, quenched with ammonoium chloride solution (20 mL), and extracted with ethyl acetate (150 mL). The organic layer was washed with saturated sodium carbonate solution (1M, 3 × 50 mL) and dried over anhydrous magnesium sulfate and solvent removed under reduced pressure. The residue was recrystallized from ethyl ether to give the desired product.

(*S*)-Benzyl (3-oxo-4-(pyridin-4-yl)butan-2-yl)carbamate 6a: yellow powder; mp 95.0−98.0 °C (44%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (br s, 2H), 7.33 (br s, 5H), 7.14−7.08 (m, 2H), 5.70 (d, J = 5.7 Hz, 1H), 5.09 (br s, 2H), 4.46 (t, J = 7.1 Hz, 1H), 3.80 (s, 2H), 1.38 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9, 155.7, 149.8, 142.1, 136.0, 128.5, 128.2, 128.0, 124.7, 67.0, 55.5, 44.9, 17.2; HRMS Calcd for $C17H_{19}N_2O_3$ $[M + H]^+$ 299.1390, found 299.1389.

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Supporting Information Available: Compound characterization data for (**3a** + **4a**), (**3b** + **4b**), (**3c** + **4c**), (**3d** + **4d**), **6b**, (**9a** + **9a′**), and **9b−e**. This material is available free of charge via the Internet at http://pubs.acs.org