Reaction of α-Amidoalkylphenyl Sulfones with Lithiated Nitriles: *Syn*-Selective Synthesis of *β*-Amino Nitriles

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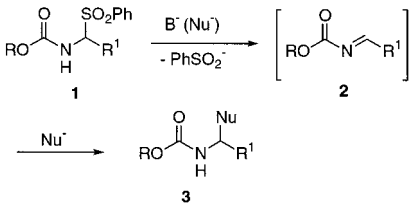
Introduction

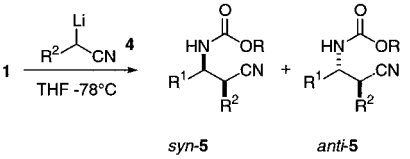
The reaction of metalated nitriles with various electrophilic substrates represents an effective procedure for introducing the cyano group into a molecular framework.[1] Lithiated nitriles efficiently add to carbonyls giving *β*-hydroxy nitriles through an aldol-like process that presents several interesting features. Recently, much attention has been focused on the diastereoselectivity of such an addition that can be carried out with high stereocontrol. The *anti*-*β*-hydroxy nitrile is usually produced under kinetic control by reaction of aldehydes with lithiated benzonitriles.[2] Addition of HMPA to the anion allows a thermodynamically controlled process that leads to a preferential formation of the *syn*-aldol derivative.[3]

A logical extension of this synthetic approach would be the utilization of imino derivatives as electrophilic substrates for metalated nitriles. However, rather surprisingly, there are only scanty reports on this kind of procedure, none of them concerning diastereoselective processes.[4] Indeed, *β*-amino nitriles are usually produced using other synthetic approaches, including aziridine ring opening,[5] conjugate addition to acrylonitrile,[6] and direct nucleophilic displacement on haloamines by cyanide anion.[7] A common drawback associated with the use of imines as substrates concerns their poor electrophilicity that often causes a preferential deprotonation with basic nucleophiles instead of a normal addition. Alternatively, reactive amidoalkylating agents[8] like *N*-acylimines can be used in the reaction with carbanionic species, but these reactive substrates are usually too unstable to be prepared and stored.

Scheme 1



Scheme 2



1a: R = Bn; R^1= $PhCH_2CH_2$
1b: R = *t*-Bu; R^1= $PhCH_2CH_2$
1c: R = Bn; R^1= *c*-C_6H_{11}
1d: R = *t*-Bu; R^1= *c*-C_6H_{11}
1e: R = Bn; R^1= $(CH_3)_2CHCH_2$
1f: R = *t*-Bu; R^1= $(CH_3)_2CHCH_2$
1g: R = *t*-Bu; R^1= Ph
1h: R = Bn; R^1= Ph

Results and Discussion

We have recently demonstrated that α-amidoalkylphenyl sulfones **1** can efficiently act as synthetic analogues of *N*-acylimines in the reaction with nucleophiles as depicted in Scheme 1.[9]

The nucleophile behaves as a base converting the sulfone **1** into the *N*-acylimine **2**, which reacts with the excess of nucleophile to give the addition product **3**.[10] Use of this procedure allowed sulfones **1** to react with lithiated nitriles **4** in THF at −78 °C to produce the corresponding *β*-amino nitriles **5** (Scheme 2, Table 1).

Lithiation of acetonitrile and arylacetonitriles can be carried out with LDA or *n*BuLi without any substantial difference in the efficiency of the subsequent nucleophilic addition. Alkanenitriles give better results with LDA as the base since the utilization of *n*BuLi at −78 °C probably

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Table 1. Synthesis of β-Amino Nitriles 5

entry	1	nitrile R^2		5	*syn:anti*[a]	yield[b] %
1	**1a**	**4a**	H	**5a**	-	70
2	**1a**	**4b**	Ph	**5b**	75:25	62
3	**1a**	**4c**		**5c**	80:20	60
4	**1a**	**4d**	2-$MeOC_6H_4$	**5d**	60:40	68
5	**1b**	**4a**	H	**5e**	-	91
6	**1c**	**4b**	Ph	**5f**	70:30	95
7	**1d**	**4b**	Ph	**5g**	70:30	77
8	**1e**	**4b**	Ph	**5h**	70:30	90
9	**1e**	**4d**	2-$MeOC_6H_4$	**5i**	60:40	90
10	**1f**	**4b**	Ph	**5j**	75:25	86
11	**1g**	**4b**	Ph	**5k**	90:10	87
12	**1h**	**4e**	1-Naphthyl	**5l**	95:5	95
13	**1h**	**4f**	Me	**5m**	70:30	60

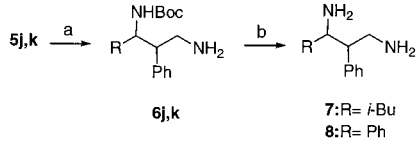
[a] Diastereomeric ratio was evaluated by ^1H NMR analysis. [b] Yields of pure, isolated products.

leads to an incomplete lithiation and, therefore, products derived from the attack of this organometallic reagent on the *N*-acylimine intermediate are found in the reaction mixture. The yields of β-amino nitriles **5** obtained are usually good when acetonitrile and arylacetonitriles are used as reagents (Table 1, entries 1−2 and 4−12) while alkanenitriles give only modest yields of the addition products **5** (Table 1, entries 3 and 14).[11] Contrary to that observed in the reaction of aldehydes,[2] α-amidoalkylphenyl sulfones **1** produce *syn*-amino nitriles **5** in a diastereoselective fashion.

This would suggest a thermodynamic control in the formation of adducts **5**, even though the stereoselectivity is either barely or not at all affected by usual factors like dilution and use of cosolvents like HMPA.[12] The preferential formation of the syn adduct could be also explained by accounting for an open-chain transition state as usually occurs with *N*-acyliminium ion intermediates.[13] However, this mechanistic pathway seems to be unlikely when lithiated carbanions react with substrates containing heteroatoms capable of coordination with the cation.[14] The preference for the syn stereoisomer is generally quite modest for most examples reported in Table 1. The best results have been obtained using sulfones **1g**,**h**, prepared from benzaldehyde, in the reaction with lithiated aryl acetonitriles **4b**,**e** (Table 1, entries 11 and 12).

Assignment of the prevailing diastereomer as syn has been accomplished by taking into account some useful remarks made by Carlier et al. on β-hydroxy nitriles.[2b] The observed chemical shifts of the α-cyano proton for the syn stereoisomer are usually higher than those of the anti one as underlined for β-hydroxy nitriles of a similar structure. Analysis of the coupling constants for the same proton also gives interesting stereochemical information.

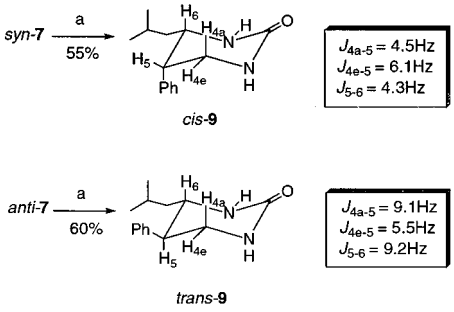
Scheme 3[a]



6j,k **7**:R= *i*-Bu **8**:R= Ph

[a]Key: a) $LiAlH_4$, $AlCl_3$, Et_2O, r.t. **6j**:73%, **6k**:75%. b) HCl, THF, r.t. **7**: 80%, **8**: 83%.

Scheme 4[a]



[a]Key: a) $(CCl_3CO)_2CO/Et_3N$, CH_2Cl_2, -78°C

Indeed, as a consequence of the favored conformation of β-amino nitriles **5** in which two large groups R and Ph are located in antiperiplanar positions, values of J_{syn} = 4.8−6.7 Hz and J_{anti} = 3.8−4.3 Hz are usually observed. Reduction of some β-amino nitriles **5** was then pursued with the aim of preparing 1,3-diamino derivatives, which are valuable intermediates in organic synthesis.[15] Among various reducing agents tested, the best results have been obtained using $LiAlH_4/AlCl_3$ in diethyl ether.[2b] Thus, β-amino nitriles **5j**,**k** have been selectively converted into the corresponding monoprotected 1,3-diamines **6** without any concurrent ring closure to the corresponding tetrahydropyrimidones (Scheme 3).[16]

Free 1,3-diamines **7** and **8** have been obtained by acidic hydrolysis of the Boc protecting group without any modification of the diastereomeric ratio with respect to β-amino nitriles **5**. The stereoisomeric mixture of diamines **7** has been efficiently separated and transformed into tetrahydropyrimidones **9** using $(CCl_3CO)_2CO/Et_3N$ in dichloromethane at −78 °C (Scheme 4).

A careful survey of the coupling constants for various protons in tetrahydropyrimidones **9** allowed us to confirm the stereochemical assignments of β-amino nitriles **5** previously described. Compound *cis*-**9**, obtained from the major diastereomer *syn*-**7**, displays a vicinal coupling constant J_{5-6} = 4.3 Hz, a value congruent with a dihedral angle of about 60°. On the other hand, *trans*-**9**, obtained from *anti*-**7**, shows for the same protons a J_{5-6} = 9.2 Hz that implies a dihedral angle of around 180°.

In conclusion, we have studied the reaction of lithiated nitriles toward α-amidoalkyphenyl sulfones that affords β-amino nitriles in good yields. These derivatives are produced with variable syn stereoselectivity depending on the nature of the substrate−reagent couple. The best results in terms of diastereoselectivity have been obtained using arylacetonitriles with α-amidoarylphenyl

(11) Other alkanenitriles tested as isobutyronitrile and methoxyacetonitrile did not give any appreciable result in the reaction with compounds **1**.

(12) A similar preference for the syn stereoisomer has been verified for the reaction of sulfones **1** with Reformatsky reagents obtained from α-halo esters; see ref 9a.

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(16) Formation of tetrahydropyrimidones at this stage has been proved to be rather troublesome since any attempt to induce a ring closure on purified amino derivatives **6** failed.

sulfones. Reduction of β-amino nitriles represents a viable method for the synthesis of 1,3-diamino derivatives.

Experimental Section

^{1}H NMR experiments were performed at 300 MHz in $CDCl_3$ as the solvent. ^{13}C NMR experiments were performed at 75 MHz in $CDCl_3$ as the solvent. Tethahydrofuran was dried by being refluxed over sodium wire and then distilled. All chemicals used are commercial. Sulfones **1** have been prepared as previously described.[9b]

General Procedure for the Preparation of β-Amino Nitriles 5. *Method A.* Arylacetonitrile **4** (5 mmol) was dissolved in THF (40 mL), and the solution was cooled at −78 °C. *n*-BuLi (5.1 mmol) was then added dropwise, and the temperature was kept at −78 °C for 30 min. Sulfone **1** (2.5 mmol) dissolved in THF (10 mL) was then added dropwise, and after 30 min at −78 °C, the reaction was quenched with saturated NH_4Cl and the mixture warmed to room temperature. The solvent was removed under reduced pressure, and the residue was extracted with CH_2Cl_2 and dried over $MgSO_4$. The crude amino nitrile obtained after removal of the solvent was purified by column chromatography (7:3 hexanes−ethyl acetate). *Method B.* Alkanenitrile **4** (5 mmol) was added to a solution of LDA (5.1 mmol) in THF (40 mL) at −78 °C. After 30 min at −78 °C, sulfone **1** (2.5 mmol) dissolved in THF (10 mL) was added dropwise and the reaction mixture was processed as described in method A.

Benzyl 1-(Cyanomethyl)-3-phenylpropyl Carbamate (5a). Yield: 70%. Mp: 93 °C. IR (cm^{-1}, KBr): 3370, 2200. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.90−2.03 (m, 2H), 2.53 (dd, 1H, J = 4.4, 16.8 Hz), 2.61−2.63 (m, 2H), 2.77 (dd, 1H, J = 5.2, 16.8 Hz), 3.78−3.96 (m, 1H), 5.03 (d, 1H, J = 8.4 Hz), 5.13 (s, 2H), 7.12−7.43 (m, 10H). Anal. Calcd for $C_{19}H_{20}N_2O_2$ (308.4): C, 74.00; H, 6.54; N, 9.08. Found: C, 74.09; H, 6.49; N, 9.03.

Benzyl 2-Cyano-1-phenylethyl-4-pyrrolidin-1-ylbutyl Carbamate (5c). Yield: 60%. Mp: 112−115 °C. IR (cm^{-1}, KBr): 3370, 2200. ^{1}H NMR (300 MHz, $CDCl_3$) syn δ: 1.60−2.05 (m, 8H), 2.35−2.90 (m, 8H), 3.12−3.22 (m, 1H), 3.95−4.10 (m, 1H), 5.14 (d, 2H, J = 2.6 Hz), 5.32 (d, 1H, J = 8.7 Hz), 7.15−7.45 (m, 10 Hz); anti δ: 1.73−1.85 (m, 6H), 1.90−2.05 (m, 2H), 2.45−2.64 (m, 4H), 2.70−2.81 (m, 4H), 2.90−3.05 (m, 1H), 4.07−4.20 (m, 1H), 5.14 (s, 2H), 5.28 (d, 1H, J = 9.9 Hz), 7.20−7.50 (m, 10H). Anal. Calcd for $C_{25}H_{31}N_3O_2$ (405.5): C, 74.04; H, 7.70; N, 10.36. Found: C, 73.99; H, 7.74; N, 10.41.

Benzyl 2-Cyano-1-cyclohexyl-2-phenylethyl Carbamate (5f). Yield: 95%. Mp: 125−128 °C. IR (cm^{-1}, KBr): 3370, 2200. ^{1}H NMR (300 MHz, $CDCl_3$) syn δ: 0.90−1.40 (m, 5H), 1.45−1.95 (m, 6H), 3.81−3.90 (m, 1H), 4.10 (d, 1H, J = 6.7 Hz), 4.96 (d, 1H, J = 9.1 Hz), 5.01 (d, 2H, J = 1.5 Hz), 7.21−7.41 (m, 10H); anti δ: 0.90−1.40 (m, 5H), 1.45−1.95 (m, 6H), 4.02−4.90 (m, 1H), 4.16 (d, 1H, J = 4.0 Hz), 4.79 (d, 1H, J = 10.1 Hz), 4.91 (d, 2H, J = 1.7 Hz), 7.21−7.41 (m, 10H). Anal. Calcd for $C_{23}H_{26}N_2O_2$ (362.5): C, 76.21; H, 7.23; N, 7.73. Found: C, 76.15; H, 7.25; N, 7.68.

***tert*-Butyl 2-Cyano-1,2-diphenylethyl Carbamate (5k).** Yield: 87%. Mp: 175−177 °C. IR (cm^{-1}, KBr): 3350, 2200. ^{1}H NMR (300 MHz, $CDCl_3$) syn δ: 1.48 (s, 9H), 4.69−4.81 (m, 1H), 5.93 (dd, 1H, J = 5.5, 7.5 Hz), 5.40 (d, 1H, J = 7.5 Hz), 7.08−7.45 (m, 10H). Anal. Calcd for $C_{20}H_{22}N_2O_2$ (322.4): C, 74.51; H, 6.88; N, 6.89. Found: C, 74.60; H, 6.84; N, 6.95.

Benzyl 2-Cyano-2-(1-naphthyl)-1-phenylethyl Carbamate (5l). Yield: 95%, oil. IR (cm^{-1}, neat): 3360, 2200. ^{1}H NMR (300 MHz, $CDCl_3$) syn δ: 5.15−5.30 (m, 1H), 5.27 (d, 2H, J = 3.7 Hz), 5.74 (d, 1H, J = 4.8 Hz), 5.81 (d, 1H, J = 5.9 Hz), 6.80−7.95 (m, 16H), 8.54 (d, 1H, J = 8.5 Hz). Anal. Calcd for $C_{27}H_{22}N_2O_2$ (406.48): C, 79.78; H, 5.46; N, 6.89. Found: C, 79.73; H, 5.50; N, 6.91.

General Procedure for the Reduction of β-Amino Nitriles 5 to Monoprotected 1,3-Diamino Derivatives 6. To a stirred suspension of $LiAlH_4$ (6.5 mmol) in diethyl ether (7 mL) was added dropwise a solution of $AlCl_3$ (6.68 mmol) in diethyl ether (7 mL) at room temperature. β-Amino nitrile **5** (2.5 mmol) dissolved in diethyl ether (7 mL) was then added, and stirring was continued for an additional 4 h. The mixture was cooled in an ice bath and treated with 3 N NaOH (8 mL), and the aqueous phase was separated and extracted with diethyl ether (4 × 15 mL). The organic phase was washed with brine and dried over $MgSO_4$; the crude product was obtained after evaporation if the solvent at reduced pressure was purified by column chromatography (92:8:0.1 dichloromethane−methanol−38% NH_4OH).

***tert*-Butyl 1-(2-Amino-1-phenylethyl)-3-methylbutyl Carbamate (6j).** Yield: 73%, oil. IR (cm^{-1}, neat): 3300. ^{1}H NMR (300 MHz, $CDCl_3$) syn δ: 0.83 (d, 3H, J = 6.7 Hz), 0.87 (d, 3H, J = 6.7 Hz), 0.95−1.05 (m, 1H), 1.08−1.18 (m, 1H), 1.41 (s, 9H), 1.52−1.68 (m, 1H), 2.69 (dt, 1H, J = 2.8, 7.1 Hz), 2.91 (dd, 1H, J = 7.1, 12.8 Hz), 3.06 (dd, 1H, J = 8.2, 12.8 Hz), 4.05−4.10 (m, 1H), 4.30 (d, 1H, J = 10.2 Hz), 7.12−7.38 (m, 5H); anti δ: 0.76 (d, 3H, J = 6.7 Hz), 0.86 (d, 3H, J = 6.7 Hz), 0.95−1.05 (m, 1H), 1.08−1.18 (m, 1H), 1.43 (s, 9H), 1.52−1.68 (m, 1H), 2.56 (dt, 1H, J = 4.9, 8.5 Hz), 2.97−3.04 (m, 2H), 3.88−3.97 (m, 1H), 4.09 (d, 1H, J = 9.5 Hz), 7.12−7.38 (m, 5H). Anal. Calcd for $C_{18}H_{30}N_2O_2$ (306.45): C, 70.55; H, 9.87; N, 9.14. Found: C, 70.49; H, 9.90; N, 9.11.

***tert*-Butyl 3-Amino-1,2-diphenylpropyl Carbamate (6k).** Yield: 75%, oil. IR (cm^{-1}, neat): 3300. ^{1}H NMR (300 MHz, $CDCl_3$) syn δ: 1.32 (s, 9H), 1.79 (bs, 2H), 2.78−3.10 (m, 3H), 4.84−5.15 (m, 2H), 7.05−7.38 (m, 10H); anti δ: 1.43 (s, 9H), 1.65 (bs, 2H), 3.05−3.32 (m, 3H), 5.66−5.80 (m, 2H), 7.05−7.40 (m, 10H). Anal. Calcd for $C_{20}H_{26}N_2O_2$ (326.44): C, 73.59; H, 8.03; N, 8.58. Found: C, 73.51; H, 7.95; N, 8.63.

General Procedure for Cleavage of *tert*-Butyl Carbamate from Derivatives 6. *N*-Boc monoprotected 1,3-diamine **6** (1.5 mmol) was dissolved in THF (10 mL), and 37% HCl (5 mL) was then added at room temperature. The mixture was stirred for 30 min at room temperature, cooled in an ice bath, and made alkaline by addition of NaOH pellets. The solution was then extracted with ethyl acetate (4 × 15 mL) and dried over Na_2SO_4. After evaporation of the solvent at reduced pressure, the crude diastereomeric mixture of diamines was separated by column chromatography (85:15:0.2 dichloromethane−methanol−37% NH_4OH).

***syn*-5-Methyl-2-phenylhexane-1,3-diamine (*syn*-7).** Yield: 60%, oil. IR (cm^{-1}, neat): 3300. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.85 (d, 3H, J = 6.4 Hz), 0.88 (d, 3H, J = 6.4 Hz), 1.10−1.14 (m, 1H), 1.17 (bs, 4H), 1.21−1−26 (m, 1H), 1.63−1.80 (m, 1H), 2.52 (dt, 1H, J = 5.9, 9.5 Hz), 2.96 (dd, 1H, J = 9.5, 12.5 Hz), 2.98−3.02 (m, 1H), 3.06 (dd, 1H, J = 5.5, 12.5 Hz), 7.20−7.35 (m, 5H). Anal. Calcd for $C_{13}H_{22}N_2$ (206.33): C, 75.68; H, 10.75; N, 13.58. Found: C, 75.73; H, 10.71; N, 13.61.

***anti*-5-Methyl-2-phenylhexane-1,3-diamine (*anti*-7).** Yield: 60%, oil. IR (cm^{-1}, neat): 3300. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.75 (d, 3H, J = 6.4 Hz), 0.79 (d, 3H, J = 6.7 Hz), 0.95−1.12 (m, 2H), 1.59−1.77 (m, 1H), 2.39 (bs, 4H), 2.54−2.63 (m, 1H), 2.98−3.08 (m, 2H), 3.18 (ddd, 1H, J = 1.2, 6.1, 12.8 Hz), 7.12−7.38 (m, 5H). Anal. Calcd for $C_{13}H_{22}N_2$ (206.33): C, 75.68; H, 10.75; N, 13.58. Found: C, 75.70; H, 10.79; N, 13.55.

***syn*-1,2-Diphenylpropane-1,3-diamine (*syn*-8).** Yield: 83%, oil. IR (cm^{-1}, neat): 3300. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (bs, 4H), 2.58−2.72 (m, 1H), 2.75−2.95 (m, 2H), 4.01 (d, 1H, J = 8.7 Hz), 7.30−7.45 (m, 10H). Anal. Calcd for $C_{15}H_{18}N_2$ (226.32): C, 79.61; H, 8.02; N, 12.38. Found: C, 79.67; H, 7.95; N, 12.44.

***cis*-4-Isobutyl-5-phenyl-tetrahydropyrimidin-2(*1H*)-one (*cis*-9).** Diamine *syn*-**7** (0.20 g, 1.0 mmol) was dissolved in dry CH_2Cl_2 (8 mL), and Et_3N (1.4 mL, 10 mmol) was then added. The solution was cooled to −78 °C, and triphosgene (0.163 g, 0.55 mmol) dissolved in CH_2Cl_2 (2 mL) was added dropwise. After 20 min, the mixture was allowed to warm to room temperature and the reaction was quenched with saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2, and the organic phase was dried over $MgSO_4$. After evaporation of the solvent at reduced pressure, the crude tetrahydropyrimidone was purified by column chromatography (30:60:10 hexanes−ethyl acetate−ethanol) giving 0.127 g (55%) of pure *cis*-**9** as a colorless oil. IR (cm^{-1}, neat): 3300. ^{1}H NMR (300 MHz, CD_3OD) δ: 0.74 (d, 3H, J = 6.7 Hz), 0.85 (d, 3H, J = 6.4 Hz), 0.90−1.01 (m, 1H), 1.17−1.26 (m, 1H), 1.58−1.74 (m, 1H), 3.24 (dt, 1H, J = 4.3, 6.1 Hz), 3.55 (d, 2H, J = 6.1 Hz), 3.71 (quint, 1H, J = 4.5 Hz), 4.83 (bs, 2H), 7.18−7.38 (m, 5H). ^{13}C NMR (75 MHz, CD_3OD) δ: 21.52, 23.39, 24.07, 40.43, 42.90, 51.97, 127.01, 128.15, 128.52, 138.94, 157.19. Anal. Calcd for $C_{14}H_{20}N_2O$ (232.32): C, 72.38; H, 8.68; N, 12.06. Found: C, 72.33; H, 8.65; N, 12.01.

***trans*-4-Isobutyl-5-phenyl-tetrahydropyrimidin-2(*1H*)-one (*trans*-9).** Diamine *anti*-**7** (0.12 g, 0.6 mmol) was dissolved in dry CH_2Cl_2 (5 mL), and Et_3N (0.85 mL, 6 mmol) was then added. The solution was cooled to −78 °C, and triphosgene (0.1 g, 0.33 mmol) dissolved in CH_2Cl_2 (1.5 mL) was added dropwise. After 20 min, the mixture was allowed to warm to room temperature and was processed as described for *syn*-**7** giving 0.083 g (60%) of pure *trans*-**9** as a white solid. Mp: 159 °C. IR (cm^{-1}, KBr): 3300. ^1H NMR (300 MHz, CD_3OD) δ: 0.80 (d, 3H, $J = 6.6$ Hz), 0.84 (d, 3H, $J = 6.6$ Hz), 1.10−1.18 (m, 1H), 1.27−1.46 (m, 1H), 1.61−1.75 (m, 1H), 2.74 (dt, 1H, $J = 5.5, 9.2$ Hz), 3.35 (dd, 1H, $J = 5.5, 12.2$ Hz), 3.40 (dd, 1H, $J = 9.2, 12.2$ Hz), 3.61 (dt, 1H, $J = 3.7, 9.2$ Hz), 4.87 (bs, 2H), 7.18−7.38 (m, 5H). ^{13}C NMR (75 MHz, CD_3OD) δ: 20.86, 23.71, 23.94, 43.14, 44.90, 45.46, 53.51, 127.47, 127.90, 128.92, 139.18, 157.57. Anal. Calcd for $C_{14}H_{20}N_2O$ (232.32): C, 72.38; H, 8.68; N, 12.06. Found: C, 72.35; H, 8.70; N, 12.03.

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Supporting Information Available: Spectral and physical data for new compounds that were not included in Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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