Peptidoyl Benzotriazolide-Mediated Acylation of Nitrile-Activated Methylene Groups

Sandhyamayee Sahu,[a] Iryna O. Lebedyeva,[a] Siva S. Panda,[a] Alan R. Katritzky*[a,b]

[a] Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA
Fax +1(352)3929199; E-mail: katritzky@chem.ufl.edu

[b] Chemistry Department, King Abdulaziz University, Jeddah 21589, Saudi Arabia

Received: 18.12.2012; Accepted after revision: 05.03.2013

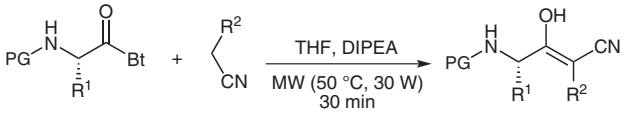
Abstract: Peptidoyl benzotriazoles permit the acylation of active methylene groups of nitriles to provide CH-acylated nitrile enols from α-amino acids or from di- or tripeptides with no loss of chirality.

Key words: acylations, cyclizations, peptides, nitriles, drugs, heterocycles

β-Keto nitriles are precursors for the synthesis of many heterocyclic compounds, such as dihydropyrans, dihydrothiopyrans, pyrazoles, pyridones, or imidazoles, and for the synthesis of specific ketones upon decyanation.[1] Reported methods for the synthesis of β-keto nitriles[2] include the base-mediated acylation of nitriles with nonactivated esters in the presence of sodium amide/liquid ammonia,[3] sodium alkoxide,[4] lithium diisopropylamide, or sodium hydride,[5] or with activated *N*-acylbenzotriazoles in the presence of butyllithium or potassium *tert*-butoxide.[6] Additionally, sterically hindered nitriles react with enolizable or nonenolizable esters in the presence of three equivalents of potassium 2,2-dimethylbutan-1-olate to give the corresponding β-keto nitriles in high yields.[7]

Elaboration of small peptides at both their N- and C-termini has been an area of interest over the past five decades.[8] Diverse functional groups and potentially bioactive residues have been introduced into native[9] or synthetic peptides[10] and into peptidomimetics[11] in efforts to expand their biological activities. Elaboration at the C-terminus has frequently been accomplished by using activated intermediates of the form COX where X is an imidazole residue,[12a,b] a succinimide residue,[13] or, advantageously, a benzotriazole (Bt) residue. 1-Peptidoyl-1*H*-1,2,3-benzotriazoles have advantages as coupling reagents in that they are sufficiently reactive to form amide bonds at ambient temperatures, they are stable enough to resist side reactions and to permit storage in the crystalline state at room temperature, and they provide good yields without detectable racemization. Thus, benzotriazole-activated N-protected amino acids and peptides have been extensively used, especially in N-, O-, and S-acylations,[14] and less frequently in C-acylations.[6,14] Several reports have demonstrated the ability of carbonyl-activated amino acids or small peptides to acylate the active methylene group of Meldrum's acid,[15] various diketones,[13] peptidyl-substituted α-keto methylenetriphenylphosphoranes,[16] or cyano esters. We recently used the benzotriazole methodology to achieve C-acylations of dimedone and cyclohexane-1,3-dione with N-protected tri- and tetrapeptidoylbenzotriazoles[14] and C-acylations of malononitrile, Meldrum's acid, and cyclohexane-1,3-dione with azido acids.[17] Here, we present an extension of this methodology to provide a convenient and efficient technique for preparing N-protected amino acids and di- and tripeptide conjugates with nitriles.

Benzotriazole derivatives **1a**–**e**, **4a**, **4b**, **6a**, and **6b**, synthesized by our previously reported method,[14] reacted with various nitriles as C-nucleophiles in the presence of 1.5 equivalents of *N*,*N*-diisopropylethylamine with microwave irradiation at 50 °C and 30 W to give good yields of the corresponding peptide conjugates **3a**–**f** (Scheme 1), **5a**, **5b** (Scheme 2), **7a**, and 7**b** (Scheme 3). Microwave irradiation of benzotriazoles **1**, **4**, and **6** in presence of nitriles **2** provided higher yields (45–90%; Table 1) than did the corresponding reactions when performed overnight at room temperature (yields ≤32%)



1a R^1 = *i*-Pr
1b R^1 = Bn
1c R^1 = CH_2(3-indolyl)
1d R^1 = H
1e R^1 = Me

2a R^2 = CN
2b R^2 = COPh
2c R^2 = COOEt

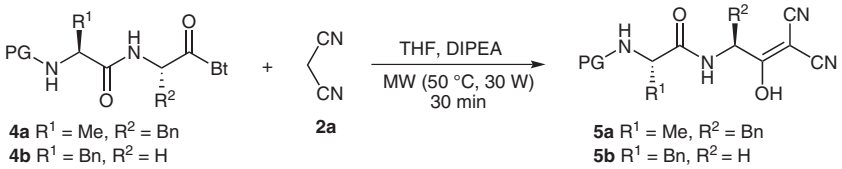
3a R^1 = *i*-Pr, R^2 = CN
3b R^1 = Bn, R^2 = CN
3c R^1 = CH_2(3-indolyl), R^2 = CN
3d R^1 = H, R^2 = CN
3e R^1 = Me, R^2 = COPh
3f R^1 = H, R^2 = COOEt

Bt = 1*H*-1,2,3-benzotriazol-1-yl

Scheme 1 Reactions of benzotriazolyl-activated N-protected amino acids with nitriles **2a**–**c**

Cyclization of the amino acid and peptide conjugates **3b**, **3d** (Scheme 4), and **5b** (Scheme 5) in 10% aqueous hydrochloric acid at room temperature gave the corresponding 2-amino-4-oxo-4,5-dihydropyrrole-3-carbonitriles **8a**–**c**, respectively, in good yields (Table 2).

SYNTHESIS 2013, 45, 1256–1260
Advanced online publication: 09.04.2013
DOI: 10.1055/s-0033-1338473; Art ID: SS-2012-M0978-OP

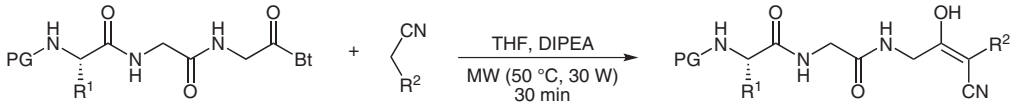


4a R^1 = Me, R^2 = Bn
4b R^1 = Bn, R^2 = H

2a

5a R^1 = Me, R^2 = Bn
5b R^1 = Bn, R^2 = H

Scheme 2 Reactions of carbonyl-activated N-protected dipeptides **4a**,**b** with malononitrile **2a**



6a R^1 = H
6b R^1 = Bn

2a R^2 = CN
2b R^2 = COPh

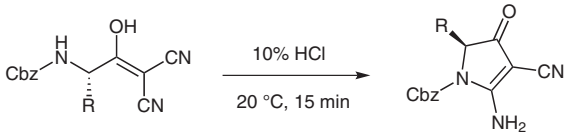
7a R^1 = H, R^2 = CN
7b R^1 = Bn, R^2 = COPh

Scheme 3 Reactions of tripeptidoylbenzotriazoles **6a** and **6b** with methylenenitriles **2a** and **2b**

Table 1 C-Acylation of N-Protected Aminoacyl, Dipeptidoyl, and Tripeptidoylbenzotriazoles

Reactant	Nitrile	Product	Yield (%)	Mp (°C)
Boc-Val-Bt[a] (**1a**)	**2a**	**3a**	68	sticky solid
Cbz-Phe-Bt (**1b**)	**2a**	**3b**	60	74-80
Cbz-Trp-Bt (**1c**)	**2a**	**3c**	85	133–137
Cbz-Gly-Bt (**1d**)	**2a**	**3d**	83	sticky solid
Cbz-Ala-Bt (**1e**)	**2b**	**3e**	45	69–71
Cbz-Gly-Bt (**1d**)	**2d**	**3f**	88	210–213
Boc-Ala-Phe-Bt (**4a**)	**2a**	**5a**	78	147–152
Cbz-Phe-Gly-Bt (**4b**)	**2a**	**5b**	90	69–74
Boc-Gly-Gly-Gly-Bt (**6a**)	**2a**	**7a**	62	135–143
Cbz-Phe-Gly-Gly-Bt (**6b**)	**2b**	**7b**	64	115–117

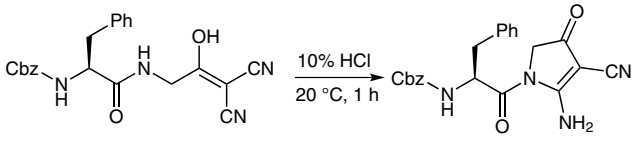
[a] Bt = 1*H*-1,2,3-benzotriazol-1-yl.



3b R = Bn
3d R = H

8a R = Bn
8b R = H

Scheme 4 Intramolecular cyclization of enols to give 2-amino-4-oxo-4,5-dihydropyrrole-3-carbonitriles **8a** and **8b**



5b

8c

Scheme 5 Synthesis of 2-amino-4-oxo-4,5-dihydropyrrole-3-carbonitrile **8c**

Table 2 2-Amino-4-oxo-4,5-dihydropyrrole-3-carbonitriles **8a**–**c**

Reactant	Product	Yield (%)	Mp (°C)
3b	**8a**	87	171–173
3d	**8b**	73	157–159[15]
5b	**8c**	87	161–163

In conclusion, N-protected aminoacyl, dipeptidoyl, and tripeptidoyl benzotriazoles are sufficiently reactive to couple with the active methylene group of nitriles under microwave irradiation at 50 °C. This offers a convenient and efficient method for the preparation of chirally pure N-protected peptide conjugates in synthetically useful yields by C-acylation. The chirality of the starting materials was preserved in the products, as demonstrated by ^{1}H and ^{13}C NMR spectroscopy and by high-performance liquid chromatographic analysis (see Supporting Information).

All the reagents were purchased from commercial sources and were used as received unless otherwise indicated. The products were purified by column chromatography on silica gel (300–400 mesh). Melting points were determined on a capillary melting-point apparatus equipped with a digital thermometer. NMR spectra were recorded in $CDCl_3$, DMSO-d_6, or CD_3OD on Mercury or Gemini NMR spectrometers operated at 300 MHz for ^{1}H (with TMS as an internal standard) or 75 MHz for ^{13}C. High-resolution mass spectra were recorded on an Agilent Technologies 6210 Time of Flight LC/MS instrument operating in the ESI mode. Elemental analyses were performed on a Carlo-Erba EA1108 instrument. All microwave-assisted reactions were carried out with a single-mode-cavity Discover Microwave Synthesizer (CEM Corporation, NC, USA). The reaction mixtures were transferred into a 10-mL glass pressure microwave tube equipped with a magnetic stirrer bar. The tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation (Discover mode: run time: 60 s; PowerMax-cooling mode).

_N_-(Aminoacyl)benzotriazoles 1a–e, 4a, 4b, 6a, and 6b; General Procedure

All the amino acid– and peptide–benzotriazole conjugates were prepared as reported previously.[18]

***tert*-Butyl ((1*S*)-2-{[(1*S*)-2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-benzyl-2-oxoethyl]amino}-1-methyl-2-oxoethyl)carbamate (4a)**

Yield: 220 mg (0.49 mmol, 67%); white solid; mp 115–117 °C.

^{1}H NMR (DMSO-d_6): δ = 8.14 (dd, J = 8.4, 0.9 Hz, 1 H), 8.06 (dd, J = 8.1, 0.9 Hz, 1 H), 7.80–7.70 (m, 1 H), 7.62–7.56 (m, 1 H), 7.49–7.43 (m, 1 H), 7.35–7.30 (m, 1 H), 7.20–6.98 (m, 4 H), 6.21–6.11 (m, 1 H), 5.20 (br s, 1 H), 4.28 (br s, 1 H), 3.44–3.38 (m, 1 H), 3.24–3.14 (m, 1 H), 1.38 (s, 9 H), 1.28 (d, J = 6.9 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 173.1, 170.5, 155.7, 146.0, 135.3, 131.1, 130.9, 129.3, 128.7, 127.4, 126.6, 120.4, 114.4, 80.5, 60.5, 54.2, 38.6, 28.4, 18.3.

Anal. Calcd for $C_{23}H_{27}N_5O_4$: C, 63.14; H, 6.22; N, 16.01. Found: C, 63.38; H, 7.01; N, 15.22.

***tert*-Butyl {2-[(2-{[2-(1*H*-1,2,3-Benzotriazol-1-yl)-2-oxoethyl]amino}-2-oxoethyl)amino]-2-oxoethyl}carbamate (6a)**

Yield: 430 mg (1.10 mmol, 64%); white solid; mp 123–124 °C.

^{1}H NMR (DMSO-d_6): δ = 8.61 (br s, 1 H), 8.27 (d, J = 6.6 Hz, 1 H), 8.24–8.15 (m, 2 H), 7.79 (br s, 1 H), 7.65–7.58 (m, 1 H), 7.06–6.98 (m, 1 H), 4.97 (d, J = 5.4 Hz, 2 H), 3.87 (d, J = 5.4 Hz, 2 H), 3.61 (d, J = 5.7 Hz, 2 H), 1.37 (s, 9 H).

^{13}C NMR (DMSO-d_6): δ = 169.9, 168.5, 155.8, 145.2, 131.0, 130.5, 126.6, 120.2, 113.7, 78.1, 43.3, 42.5, 41.7, 28.2.

Anal. Calcd for $C_{17}H_{22}N_6O_5$: C, 52.30; H, 5.68; N, 21.53. Found: C, 51.84; H, 5.55; N, 22.08.

Nitriles 3a–f, 5a, 5b, 7a, and 7b; General Procedure

A dry, heavy-walled, Pyrex tube equipped with a small stirrer bar was charged with a solution of the appropriate benzotriazole intermediate (1 equiv), C-nucleophile (1 equiv), and DIPEA (1.5 equiv) in THF (5 mL). The mixture was exposed to microwave irradiation (50 °C, 30 W) for the appropriate time with simultaneous cooling. When the reaction was complete (TLC), the THF was evaporated and the reside was acidified with 2 M HCl, then extracted with EtOAc (3 × 20 mL). The solvent was evaporated under reduced pressure, and the residue was purified by crystallization (EtOAc).

***tert*-Butyl [(1*S*)-3,3-Dicyano-1-isopropyl-2-oxopropyl]carbamate (3a)**

Yield: 141 mg (0.53 mmol, 68%); sticky light-orange solid.

^{1}H NMR (DMSO-d_6): δ = 6.00 (d, J = 8.1 Hz, 1 H), 4.11 (br s, 1 H), 1.85 (br s, 1 H), 1.36 (s, 9 H), 0.84 (d, J = 6.3 Hz, 3 H), 0.74 (d, J = 5.7 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 191.0, 155.1, 121.9, 120.5, 77.7, 58.8, 46.4, 31.1, 28.2, 19.5, 17.6.

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{13}H_{18}N_3O_3$: 264.1356; found: 264.1354.

Benzyl [(1*S*)-1-Benzyl-3,3-dicyano-2-hydroxyprop-2-en-1-yl]carbamate (3b)

Yield: 130 mg (0.37 mmol, 60%); white solid; mp 74–80 °C.

^{1}H NMR (DMSO-d_6): δ = 7.33–7.20 (m, 10 H), 4.90 (s, 2 H), 4.48–4.44 (m, 1 H), 2.92–2.63 (m, 2 H).

^{13}C NMR (DMSO-d_6): δ = 190.9, 155.6, 138.7, 137.2, 129.1, 128.2, 127.9, 127.6, 127.4, 126.1, 122.1, 120.6, 65.0, 57.1, 44.9, 40.4, 38.0.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{20}H_{17}N_3NaO_3$: 370.1162; found: 370.1160.

Benzyl [(1*S*)-3,3-Dicyano-2-hydroxy-1-(1*H*-indol-3-ylmethyl)prop-2-en-1-yl]carbamate (3c)

Yield: 187 mg (0.48 mmol, 85%); light-orange solid; mp 133–137 °C.

^{1}H NMR (DMSO-d_6): δ = 10.75 (s, 1 H), 7.72 (d, J = 8.1 Hz, 1 H), 7.33–6.90 (m, 10 H), 4.93 (d, J = 13.2 Hz, 1 H), 4.86 (d, J = 12.6 Hz, 1 H), 4.60–4.42 (m, 1 H), 3.05 (dd, J = 14.3 Hz, 3.5 Hz, 1 H), 2.78 (dd, J = 14.4 Hz, 10.2 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 191.8, 155.6, 137.2, 136.1, 128.3, 127.6, 127.5, 124.0, 122.4, 120.7, 118.7, 118.2, 111.2, 110.7, 65.0, 59.2, 56.0, 28.2.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{22}H_{18}N_4NaO_3$: 409.1271; found: 409.1268.

Benzyl (3,3-Dicyano-2-hydroxyprop-2-en-1-yl)carbamate (3d)

Yield: 170 mg (0.67 mmol, 83%); light-yellow sticky solid.

^{1}H NMR (DMSO-d_6): δ = 7.43–7.29 (s, 5 H), 7.05 (br s, 1 H), 5.01 (s, 2 H), 3.74 (d, J = 5.7 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 187.5, 156.3, 137.2, 128.3, 127.7, 127.7, 127.1, 121.9, 120.5, 65.3, 59.8, 45.4.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{12}N_3O_3$: 258.0873; found: 258.0861.

Benzyl [(1*S*,2*E*)-3-Cyano-2-hydroxy-1-methyl-4-oxo-4-phenylbut-2-en-1-yl]carbamate (3e)

Yield: 121 mg, (0.34 mmol, 45%); orange solid; mp 69–71 °C.

^{1}H NMR (DMSO-d_6): δ = 7.69–7.66 (m, 1 H), 7.51–7.31 (m, 9 H), 5.02 (s, 2 H), 5.02–4.88 (m, 1 H), 1.29–1.24 (m, 3 H).

^{13}C NMR (DMSO-d_6): δ = 194.3, 187.8, 155.1, 142.6, 137.2, 129.2, 128.3, 127.6, 127.4, 124.5, 83.1, 65.1, 52.3, 19.0.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{20}H_{18}N_2NaO_4$: 373.1159; found: 373.1161.

Ethyl 4-{[(Benzyloxy)carbonyl]amino}-2-cyano-3-oxobutanoate (3f)

Yield: 215 mg, (0.33 mmol, 88%); white solid; mp 210–213 °C.

^{1}H NMR (DMSO-d_6): δ = 7.35 (s, 5 H), 6.66 (s, 1 H), 5.00 (s, 2 H), 4.04–3.91 (m, 4 H), 1.12 (t, J = 6.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 188.2, 168.7, 156.7, 138.0, 129.0, 128.3, 123.3, 71.0, 65.8, 57.8, 48.6, 15.6.

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{15}H_{15}N_2O_5$: 303.0986; found: 303.0987.

***tert*-Butyl ((1*S*)-2-{[(1*S*)-1-Benzyl-3,3-dicyano-2-hydroxyprop-2-en-1-yl]amino}-1-methyl-2-oxoethyl)carbamate (5a)**

Yield: 172 mg (0.45 mmol, 78%); white solid; mp 147–152 °C.

^{1}H NMR (DMSO-d_6): δ = 7.54 (d, J = 8.1 Hz, 1 H), 7.19–7.16 (m, 5 H), 6.95 (br s, 1 H), 4.72 (br s, 1 H), 3.92–3.82 (m, 1 H), 2.93–2.68 (m, 2 H), 1.37 (s, 9 H), 1.07 (d, J = 7.5 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 192.6, 174.0, 156.6, 137.7, 129.8, 128.4, 126.7, 121.3, 119.6, 80.0, 60.8, 55.3, 51.0, 39.4, 28.0, 17.7.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{20}H_{24}N_4NaO_4$: 407.1690; found: 407.1689.

Benzyl {(1*S*)-1-Benzyl-2-[(3,3-dicyano-2-hydroxyprop-2-en-1-yl)amino]-2-oxoethyl}carbamate (5b)

Yield: 200 mg (0.50 mmol, 90%); light-orange solid; mp 69–74 °C.

^{1}H NMR (DMSO-d_6): δ = 7.91 (br s, 1 H), 7.55 (d, J = 8.7 Hz, 1 H), 7.32–7.19 (m, 10 H), 4.93 (s, 2 H), 4.39–4.20 (m, 1 H), 3.84 (d, J = 4.8 Hz, 2 H), 3.04–3.02 (m, 1 H), 2.79–2.62 (m, 1 H).

^{13}C NMR (DMSO-d_6): δ = 186.9, 171.5, 155.9, 138.3, 137.1, 129.3, 128.4, 128.1, 127.7, 127.4, 126.3, 121.7, 120.3, 65.3, 56.4, 44.9, 44.1, 37.6.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{20}N_4NaO_4$: 427.1377; found: 427.1366.

tert-Butyl [2-({2-[(3,3-Dicyano-2-hydroxyprop-2-en-1-yl)amino]-2-oxoethyl}amino)-2-oxoethyl]carbamate (7a)

Yield: 134 mg (0.39 mmol, 62%); dark-orange solid; mp 135–143 °C.

^{1}H NMR (DMSO-d_6): δ = 8.02 (br s, 1 H), 7.78 (br s, 1 H), 7.00 (br s, 1 H), 3.80 (d, *J* = 5.1 Hz, 2 H), 3.72 (d, *J* = 5.4 Hz, 2 H), 3.57 (d, *J* = 5.7 Hz, 2 H), 1.38 (s, 9 H).

^{13}C NMR (DMSO-d_6): δ = 186.8, 169.6, 168.5, 155.8, 121.7, 120.3, 78.1, 59.8, 43.9, 43.3, 41.9, 28.2.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{14}H_{19}N_5NaO_5$: 360.1278; found: 360.1268.

Benzyl {(1*S*)-1-Benzyl-2-[(2-{[(2*Z*)-3-cyano-2-hydroxy-4-oxo-4-phenylbut-2-en-1-yl]amino}-2-oxoethyl)amino]-2-oxoethyl}carbamate (7b)

Yield: 170 mg, (0.31 mmol, 64%); orange solid; mp 115–117 °C.

^{1}H NMR (DMSO-d_6): δ = 8.38 (br s, 1 H), 8.13 (br s, 1 H), 7.77 (d, *J* = 7.2 Hz, 2 H), 7.62–7.45 (m, 3 H), 7.39–7.02 (m, 12 H), 4.94 (s, 2 H), 4.42–4.21 (m, 3 H), 3.87–3.67 (m, 2 H), 3.15–2.98 (m, 1 H), 2.83–2.65 (m, 1 H).

^{13}C NMR (DMSO-d_6): δ = 194.6, 185.9, 171.9, 169.0, 155.9, 138.2, 137.0, 135.4, 132.0, 129.2, 128.4, 128.3, 128.1, 127.6, 127.4, 126.3, 126.2, 119.1, 86.9, 65.2, 56.2, 46.8, 41.9, 37.5.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{30}H_{28}N_4NaO_6$: 563.1901; found: 563.1902.

2-Amino-4-oxo-4,5-dihydropyrrole-3-carbonitriles 8a–c; General Procedure

10% aq HCl (1 mL) was added to a solution of **3b**, **3d** or **5b** (1 equiv) in EtOAc (5 mL). The mixture was stirred vigorously for 15 min to 1 h at 25 °C and then the organic layer was separated and concentrated under vacuum.

Benzyl (2*S*)-5-Amino-2-benzyl-4-cyano-3-oxo-2,3-dihydro-1*H*-pyrrole-1-carboxylate (8a)

Yield: 217 mg (0.62 mmol, 87%); white solid; mp 171–173 °C.

^{1}H NMR (DMSO-d_6): δ = 9.21 (br s, 1 H), 8.51 (s, 1 H), 7.56–7.39 (m, 5 H), 7.16 (m, 3 H), 6.78 (s, 2 H), 5.44 (d, *J* = 12.0 Hz, 1 H), 5.32 (d, *J* = 11.4 Hz, 1 H), 4.45 (d, *J* = 3.0 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 188.6, 166.2, 150.9, 134.9, 134.2, 129.2, 129.1, 128.7, 128.6, 128.0, 126.8, 113.5, 72.0, 68.5, 64.5, 34.9.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{17}N_3NaO_3$: 370.1162; found: 370.1173.

Benzyl 5-Amino-4-cyano-3-oxo-2,3-dihydro-1*H*-pyrrole-1-carboxylate (8b)

Yield: 182 mg (0.76 mmol, 73%); white solid; mp 157–159 °C.

^{1}H NMR (DMSO-d_6): δ = 9.47 (br s, 1 H), 8.65 (br s, 1 H), 7.45–7.33 (m, 5 H), 5.27 (s, 2 H), 4.11 (s, 2 H).

^{13}C NMR (DMSO-d_6): δ = 186.7, 166.5, 150.8, 135.0, 128.4, 128.2, 127.7, 113.8, 72.0, 67.9, 53.8.

HRMS (ESI): *m/z* [M + Na]$^+$calcd for $C_{13}H_{11}N_3NaO_3$: 280.0693; found: 280.0697.

Benzyl [(1*S*)-2-(5-Amino-4-cyano-3-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)-1-benzyl-2-oxoethyl]carbamate (8c)

Yield: 217 mg (0.54 mmol, 87%); white solid; mp 161–163 °C.

^{1}H NMR (DMSO-d_6): δ = 7.96 (br s, 1 H), 7.56 (d, *J* = 9.0 Hz, 1 H), 7.40–7.18 (m, 10 H), 4.93 (br s, 2 H), 4.3 (br s, 1 H), 3.89–3.80 (m, 2 H), 3.12–2.92 (m, 1 H), 2.80–2.70 (m, 1 H).

^{13}C NMR (DMSO-d_6): δ = 186.9, 171.4, 155.9, 138.3, 137.0, 129.2, 128.3, 128.0, 127.6, 127.4, 126.2, 65.2, 56.2, 46.7, 43.9, 37.5.

HRMS (ESI): *m/z* [M + Na]$^+$calcd for $C_{22}H_{20}N_4NaO_4$: 427.1377; found: 427.1371.

Acknowledgment

We thank the University of Florida, The Kenan Foundation, and King Abdulaziz University, Jeddah, Saudi Arabia, for financial support. We also thank to Dr. C. D. Hall, Mrs. G. Vakulenko, and Mr. Z. Wang for reading the manuscript.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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