Solid-Phase Synthesis of Novel Heterocycles Containing Thiohydantoin and Isoxazole Rings

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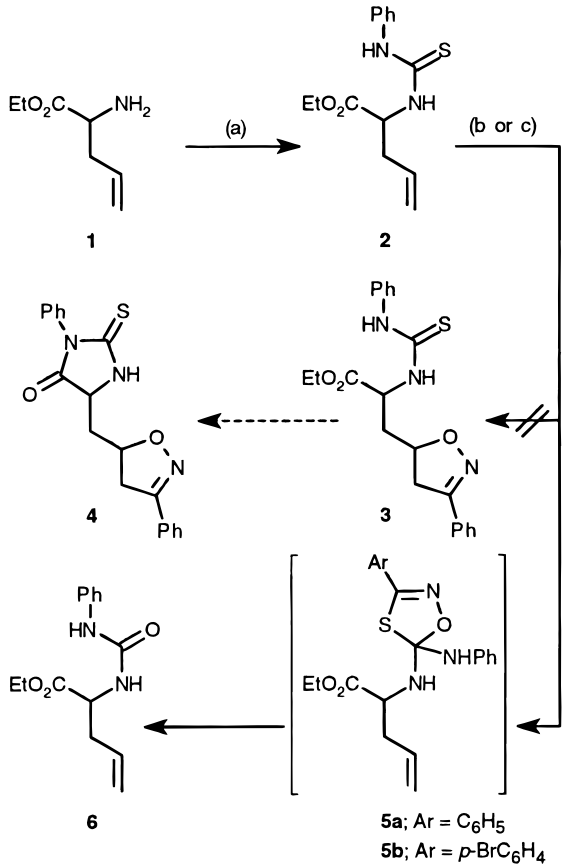
Recently, much attention has been directed toward solid-phase methods development for the synthesis of heterocycles[1] such as hydantoins[2] for use in biological discovery efforts. Indeed, the hydantoin scaffold has a rich history with both pharmaceutical[3] and agricultural[4] applications. Given the diversity potential of the hydantoin scaffold, it is suprising that there are very few reports of solid-phase routes to thiohydantoins.[5] As part of our efforts toward the preparation and biological evaluation of hydantoin-containing heterocycles, we disclose here (i) an efficient route for the synthesis of novel isoxazole-containing thiohydantoins, (ii) evidence for thiourea → urea interconversion mediated by nitrile oxides, and (iii) a synthetic strategy applicable to solid-phase combinatorial approaches.

In a previous report, we disclosed a route to isoxazolohydantoins,[6] but efforts to extend this chemistry to the synthesis of isoxazolidinothiohydantoins (**4**) proved unsuccessful (Scheme 1). Upon closer examination, we found that the attempted 1,3-dipolar cycloaddition reaction of thiourea intermediate **2** gave urea **6** upon treatment with a Mukaiyama-generated nitrile oxide[7] (generated in situ). None of the anticipated isoxazolidinothiourea intermediate **3** was detected. After numerous trials, we concluded that the Mukaiyama-mediated conversion of **2** to **3** was not practical.

In light of this result with **2**, we were intriuged by the report that benzophenones are obtained upon treatment of thiobenzophenones with benzonitrile *N*-oxides.[8] The transient intermediacy of a 1,4,2-oxathiazoline heterocycle was proposed to account for this result. By analogy, **2** → **6** may proceed via the addition product 1,4,2-oxathiazoline **5a** with subsequent rearrangement yielding **6** (and presumably PhNCS). On the other hand, we wondered if an isocyanate/isothiocyanate exchange process was operative (i.e., involving the addition of Mukaiyama dehydrating agent PhNCO to thiourea **2**). This possibility was ruled out by treating **2** with phenyl isocyanate and Et_3N (cat.) with recovery of unreacted thiourea (**2**). That a 1,4,2-oxathiazoline intermediate was involved was established by treating **2** with *p*-BrC_6H_4-CH=NOH and bleach (the Huisgen method for in situ nitrile oxide generation)[9] and again obtaining urea **6** (and presumably *p*-$BrPC_6H_4NCS$) by the rearrangement of 1,4,2-oxathiazoline **5b**.

Scheme 1. Failed Attempt To Prepare Isoxazolidinothiohydantoin 4 from Thiourea 2[a]



[a] (a) PhNCS, CH_2Cl_2, rt; (b) $PhCH_2NO_2$, PhNCO (2 equiv), Et_3N (cat.), THF, 60 °C; (c) *p*-BrC_6H_4CH=NHOH, bleach, CH_2Cl_2, 0 °C.

On the basis of these results with **2**, our wish to avoid the formation of diastereomers (vis-à-vis the two stereogenic centers in **4**), and the desire to introduce additional diversity at N1 of the thiohydantoin heterocycle, our original solid-phase plan (route A, Scheme 2) for the preparation of isoxazolidinothiohydantoins **4** from **7** was modified to route B and the preparation of isoxazolothiohydantoins **12** starting from **8**. Thus, the alkyne moiety of resin bound amino ester **8** afforded isoxazole derivatives **9** via a Mukaiyama-generated nitrile oxide 1,3-dipolar cycloaddition (two nitroalkanes were employed in this first diversification step; R^1). Deprotection of the Boc group followed by reductive *N*-alkylation of the

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(3) (a) Ware, E. *Chem. Rev.*, **1950**, *46*, 403. (b) Spinks, A.; Waring, W. S. *Prog. Med. Chem.* **1963**, *3*, 313. (c) Karolakwojciechowska, J.; Kwiatkowski, W.; Kieckonono, K. *Pharmazie* **1995**, *50*, 114. (d) Brouillette, w. J.; Jestkov, V. P.; Brown, M. L.; Akhtar, M. S. *J. Med. Chem.* **1994**, *37*, 3289. (e) Brouillette, W. J.; Brown, G. B.; Deloreg, T. M.; Liang, G. *J. Pharm. Sci.* **1990**, *79*, 871.
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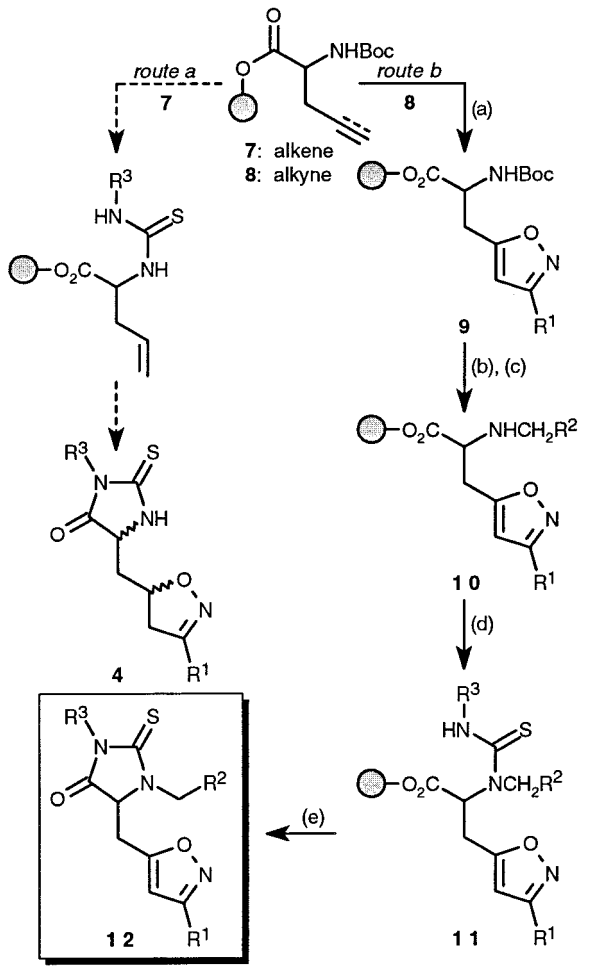
Scheme 2. Solid-Phase Synthesis of Isoxazolothiohydantoins 12[a]



[a] (a) $R^1CH_2NO_2$, PhNCO, Et_3N, THF; (b) THF/CH_2Cl_2 (1:1); then aq HCl; then aq NaOH; (c) R_2CHO, $NaCNBH_3$, AcOH; (d) R_3NCS; (e) 60 °C, THF.

primary amino moiety[10] with a variety of aldehydes (three aldehydes were employed in this second diversification step; R^2) afforded resins **10**. Finally, the third element of diversity was introduced by *N*-acylating the resulting secondary amine with various isothiocyanates (three; R^3) to deliver **11**. Resin release was accomplished by simply warming a THF suspension of resin **11** to give a total of 18 different isoxazolothiohydantoins (**12**) (see Table 1). These solid-phase reactions were all accomplished with the aid of a Quest 210 Manual Synthesizer.

Since thiourea resin **11** can be so readily cyclized to the final product, it is desirable to use the isothiocyanate as the limiting reagent to simplify isolation of the final product **12** from the reaction mixture. If excess isothiocyanate is used (up to 3 equiv), product purification by passing through a short bed of silica gel is quite effective since most isothiocyanates have high R_f values while most isoxazolothiohydantoins have low R_f values (often in the range of ≈0.9 versus ≈0.1, respectively). Furthermore, remaining isothiocyanate generally equilibrates very slowly to its thiourea (isocyanate equilibrate to the corresponding urea much more rapidly), and the reaction mixture is generally not contaminated by thioureas. Alternatively, remaining isothiocyanates can be easily removed by use of solid-supported scavengers[12] such as aminomethylpolystyrene.

Table 1. Substituted Isoxazolothiohydantoins 12

entry	R_1	R_2	R_3	yield[a] (%)
12a	ethyl	phenyl	phenyl	34
12b	ethyl	phenyl	3-chlorophenyl	30
12c	ethyl	phenyl	4-chlorophenyl	32
12d[b]	ethyl	3,5-dimethoxy phenyl	phenyl	35
12e	ethyl	3,5-dimethoxy phenyl	3-chlorophenyl	37
12f	ethyl	3,5-dimethoxy phenyl	4-chlorophenyl	32
12g	ethyl	2-thienyl	phenyl	40
12h	ethyl	2-thienyl	3-chlorophenyl	36
12i	ethyl	2-thienyl	4-chlorophenyl	35
12j[b]	phenyl	phenyl	phenyl	30
12k	phenyl	phenyl	3-chlorophenyl	32
12l[b]	phenyl	phenyl	4-chlorophenyl	38
12m	phenyl	3,5-dimethoxy phenyl	phenyl	36
12n[b]	phenyl	3,5-dimethoxy phenyl	3-chlorophenyl	31
12o[b]	phenyl	3,5-dimethoxy phenyl	4-chlorophenyl	30
12p	phenyl	2-thienyl	phenyl	37
12q[b]	phenyl	2-thienyl	3-chlorophenyl	38
12r	phenyl	2-thienyl	4-chlorophenyl	39

[a] Overall yield from the resin **8**.[11] [b] After random selection, these compounds were fully characterized: see Experimental Section. The remaining compounds of general structure **12** were characterized by ^{1}H NMR and ^{13}C NMR.

Boc-protected amino ester resin **8** was synthesized as depicted in Scheme 3. The condensation of glycine ethyl ester•HCl with benzophenone imine gave benzophenone Schiff base **13**.[13] Subsequent alkylation with propargyl chloride gave protected amino ester **14** which, upon imine hydrolysis with aq HCl and neutralization of the resulting ammonium salt with aq NaOH, delivered **15**. Boc-protection of the amino moiety (**16**) followed by saponification and neutralization produced Boc-protected amino acid **17** which was coupled with hydroxypropyloxymethylpolystyrene[14] (from reaction of Merrifield resin with the alkoxide of 1,3-propanediol) in the presence of DIC to give resin **8** (Scheme 3).

In summary, we have established a viable route for the synthesis of novel isoxazole- and thiohydantoin-containing heterocycles via solid-phase organic chemistry. A demonstration library of 18 of these compounds has been prepared using a Quest 210 Manual Synthesizer. Production of large library of these heterocycles via parallel solid phase reaction and evalulation of their biological activitives are currently under investigation.

Experimental Section

Ethyl 2-{[(Phenylamino)thioxomethyl]amino}pent-4-enoate (2). Ethyl 2-aminopent-4-enoate **1** (0.2 g, 1.39 mmol) was treated with phenyl isothiocyanate (0.188 g, 1.39 mmol) in CH_2Cl_2 (10 mL) for 4 h at ambient temperature. The solvent was removed at reduced pressure, and short-pass column chromatography (silica gel, EtOAc:hexane = 1:3) of the residue afforded the desired compound **2** (0.348 g, 1.25 mmol, 90%) as a yellow oil: FTIR (neat) 3198, 2977, 1727, 1523, 1189 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.46−7.39 (m, 2H), 7.36−7.22 (m, 3H), 6.78 (d, 1H, J = 7.6 Hz), 5.70−5.57 (m, 1H), 5.21 (dd, 1H, J = 13.1, 5.6 Hz), 5.07 (s, 1H), 5.02 (d, 1H, J = 5.1 Hz), 4.17 (q, 2H, J = 7.1 Hz), 2.77−2.71 (m, 1H), 2.68−2.54 (m, 1H),

(11) The loading of resin **8** was determined to be 2 mmol (Boc)/g by obtaining the Boc acid **17** from the hydrolysis of the resin **8**.

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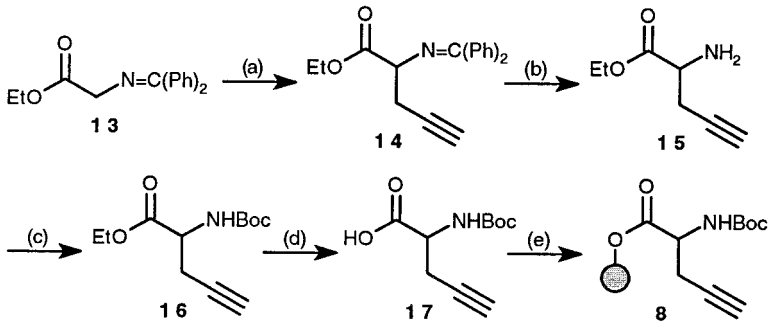
Scheme 3. Preparation of Resin 8[a]



[a] (a) NaH, HC≡CCH$_2$Cl, THF/DMF (10:1), rt; (b) aq HCl; then aq NaOH; (c) (Boc)$_2$O, CH$_2$Cl$_2$, rt; (d) aq NaOH; then aq HCl; (e) PS−O(CH$_2$)$_3$OH, DIC, DMAP, CH$_2$Cl$_2$/DMF (4:1).

1.25 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 179.7, 171.4, 136.1, 131.8, 129.6, 126.6, 124.4, 119.0, 61.3, 56.6, 36.0, 13.9.

Ethyl 2-[(Phenylamino)carbonylamino]pent-4-enoate (6) from 1. Ethyl 2-aminopent-4-enoate **1** (0.2 g, 1.39 mmol) was treated with phenyl isocyanate (0.165 g, 1.39 mmol) in CH$_2$Cl$_2$ (10 mL) for 2 h at ambient temperature. The solvent was removed at reduced pressure. Column chromatography (silica gel, EtOAc:hexane = 1:4) of the residue afforded the desired compound **6** (0.346 g, 1.32 mmol, 95%) as a white solid: mp 233−235 °C; FTIR (KBr) 3207, 2983, 1740, 1652, 1553, 1497 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.82 (s, 1H), 7.37−7.17 (m, 4H), 6.97 (t, 3H, J = 7.2 Hz), 6.18 (d, 1H, J = 7.8 Hz), 5.75−5.66 (m, 1H), 5.11−5.04, (m 2H), 4.62 (dd, 1H, J = 13.4, 6.4 Hz), 4.21−4.10 (m, 2H), 2.59−2.46 (m, 2H), 1.22 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 172.5, 155.8, 138.7, 132.4, 128.6, 122.6, 119.7, 118.5, 61.1, 52.4, 36.6, 13.9.

Ethyl 2-[(Phenylamino)carbonylamino]pent-4-enoate (6) from 2. To a solution of thiourea **2** (0.3 g, 1.07 mmol) in THF (20 mL) was added phenyl isocyanate (0.256 g, 2.15 mmol), α-nitrotoluene (0.146 g, 1.07 mmol), and Et$_3$N (10 mg, 0.10 mmol). The reaction mixture was stirred for 10 h at room temperature and then refluxed overnight. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel, EtOAc:hexane = 1:9) to give **6** (0.151 g, 0.57 mmol, 54%) as a white solid (see data in preceding paragraph).

Ethly 2-Aminopent-4-ynoate (15). To the solution of benzophenone Schiff base **13** (5 g, 18.70 mmol) in THF/DMF (60 mL/15 mL) was added NaH (0.49 g, 20.57 mmol) under nitrogen. The reaction mixture was stirred for 10 min, followed by the addition of propargyl chloride (1.41 g, 18.70 mmol), and stirred for 8 h at ambient temperature. Ethyl acetate (100 mL) was added to the reaction mixture, which was washed with water (30 mL × 3) and dried with anhydrous MgSO$_4$. Removal of solvent under reduced pressure gave 5.25 g of crude unstable intermediate **14**.

A solution of **14** in THF (50 mL) was treated with 1 N HCl to adjust the pH to ≈4 and stirred for 5 min. Ethyl acetate (50 mL) and water (30 mL) were added to the reaction mixture, and the aqueous layer was neutralized with 1 N NaOH (pH ≈9) and extracted with ethyl acetate (20 mL x 5). The organic layer was dried with anhydrous MgSO$_4$. Removal of solvent under reduced pressure, followed by column chromatography (silica gel, EtOAc:hexane = 1:5), afforded **15** (1.97 g, 14.02 mmol, 75%) as a yellow oil: FTIR (neat) 3382, 3290, 2980, 1729, 1192 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.24−4.17 (m, 2H), 3.61 (t, 1H, J = 5.5 Hz), 2.62 (ddd, 1H, J = 5.5, 2.5, 2.5 Hz), 2.11 (t, 1H, J = 2.5 Hz), 1.31 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.2, 79.4, 70.7, 60.7, 52.9, 24.5, 13.8.

Ethyl 2-[(*tert*-Butoxy)carbonylamino]pent-4-ynoate (16). To a solution of **15** (3 g, 21.27 mmol) in CH$_2$Cl$_2$ (50 mL) was added di-*tert* -butyl dicarbonate (4.64 g, 21.27 mmol) at 0 °C, and the reaction mixture was stirred overnight at room temperature. Removal of solvent under reduced pressure and short-pass column chromatography (silica gel, EtOAc:hexane = 1:5) afforded **16** (4.71 g, 19.54 mmol, 92%) as a colorless oil: FTIR (neat) 3308, 2979, 1719, 1500, 1158 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.47 (d, 1H, J = 8.0 Hz), 4.35 (m, 1H), 4.14 (m, 2H), 2.65 (m, 2H), 2.02 (t, 1H, J = 2.4 Hz), 1.37 (s, 9H), 1.21 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.2, 154.8, 79.6, 78.5, 71.3, 61.2, 52.0, 28.0, 22.4, 13.8.

2-[(tert-Butoxy)carbonylamino]pent-4-ynoic acid (17). To a solution of **16** (5 g, 20.7 mmol) in EtOH/H$_2$O (20 mL/20 mL) was added NaOH (1.66 g, 41.5 mmol) at 0 °C. The reaction mixture was stirred overnight at room temperature, extracted with ether (30 mL x 3), and dried with anhydrous MgSO$_4$. Removal of the solvent under reduced pressure followed by the recrystallization (EtOAc and hexane) afforded **17** (3.6 g, 15.90 mmol, 81%) as a white solid: Mp 97−98 °C; FTIR (neat) 3330, 2979, 1708, 1509 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 11.98 (s, 1H), 5.42 (s, br, 1H), 4.53 (m, 1H), 2.79 (m, 2H), 2.08 (s, 1H), 1.46 (S, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.0, 155.4, 80.7, 78.3, 71.9, 51.8, 28.3, 22.5. Anal. Calcd for C$_{10}$H$_{15}$NO$_4$: C, 56.32; H, 7.09; N, 6.56. Found: C, 56.40; H, 7.12; N, 6.54.

General Procedure for the Synthesis of Thiohydantoins 12a−r (12j). A solution of DMAP (0.195 g, 1.6 mmol) in DMF/CH$_2$Cl$_2$ (6 mL/24 mL) was prepared. Acid **17** (3.4 g, 16 mmol) and DIC (2.01 g, 16 mmol) were dissolved in DMF/CH$_2$Cl$_2$ (6 mL/24 mL), and this solution was added to the flask which contained the hydroxypropyloxymethylpolystyrene resin (4 g, 8 mmol). Finally, the DMAP solution was added, and the reaction mixture was stirred overnight at ambient temperature. The resin was washed with DMF, CH$_2$Cl$_2$, and ether and dried to give the resin **8**.

Resin **8** (4 g) was swollen in THF (100 mL), and α-nitrotoluene (3.29 g, 24 mmol), phenyl isocyanate (5.71 g, 48 mmol), and Et$_3$N (0.12 mL) were added. The reaction mixture was stirred at 60 °C overnight and then washed with DMF, THF, and ether. Drying in vacuo gave resin **9** (R^1 = Ph) which was treated with 50% TFA/CH$_2$Cl$_2$(30 mL) at ambient temperature for 1 h. The resin was washed with DMF and CH$_2$Cl$_2$, followed by treatment with 10% Et$_3$N in CH$_2$Cl$_2$ (30 mL) for 1 h. The resulting resin was washed with DMF, CH$_2$Cl$_2$, and ether and dried under vacuum to give the free amine functional group attached resin.

This resin (0.2 g scale) was treated with the benzaldehyde (0.195 g, 1.8 mmol) in TMOF/THF (5 mL/5 mL) for 2 h at ambient temperature and then washed with TMOF/THF (1:1). Subsequent addition of NaCNBH$_3$ (48 mg, 0.76 mmol) in THF/MeOH/AcOH (9 mL/1 mL/0.1 mL) and agitating overnight at ambient temperature, followed by washes with MeOH/THF (1:3), MeOH/DMF (1:3), DMF, and CH$_2$Cl$_2$, gave resin **10** which was dried under nitrogen.

Resin **10** was treated with phenyl isothiocyanate (0.162 g, 1.2 mmol) in THF (10 mL) at 60 °C overnight to sequentially effect thiourea formation (giving **11**) and cycloelimination to produce isoxazolothiohydantoin **12j**. The resin was washed with THF, and the combined organic solvent was evaporated under reduced pressure. The resulting residue was purified by short-pass column chromatography (R_f values: phenyl isothicyanate, 0.95; product, 0.05 in hexane) to give 52 mg of **12j**.

4-[(3,4-Dimethoxyphenyl)methyl]-3-[(3-ethylisoxazol-5-yl)methyl]-1-phenyl-5-thioxopyrrolidin-2-one (12d). Mp 111−112 °C; FTIR (KBr) 3008, 2965, 1751, 1603, 1464 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.51−7.42 (m, 3H), 7.23−7.20 (m, 2H), 6.96 (d, 1H, J = 1.5 Hz), 6.89−6.82 (m, 2H), 5.85 (s, 1H), 5.66 (d, 1H,

J = 14.9 Hz), 4.50 (d, 1H, J = 14.9 Hz), 4.35 (t, 1H, J = 4.4 Hz), 3.88 (s, 3H), 3.85 (s, 3H), 3.41 (d, 2H, J = 4.4 Hz), 2.65 (q, 2H, J = 7.6 Hz), 1.23 (t, 3H, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.9, 171.3, 165.3, 165.2, 149.4, 149.2, 133.2, 129.2, 129.0, 128.2, 127.1, 120.7, 111.6, 111.1, 102.6, 59.4, 55.9, 55.8, 48.7, 26.9, 19.4, 12.5. Anal. Calcd for $C_{24}H_{25}N_3O_4S$: C, 63.84; H, 5.58; N, 9.30. Found: C, 63.57; H, 5.60; N, 9.21.

1-Phenyl-3-[(3-phenylisoxazol-5-yl)methyl]-4-benzyl-5-thioxopyrrolidin-2-one (12j). Mp 193−194 °C; FTIR (KBr) 3055, 2938, 1754, 1603, 1467 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77−7.73 (m, 2H), 7.47−7.39 (m, 5H), 7.37 (s, 5H), 7.35−7.20 (m, 3H), 6.29 (s, 1H), 5.84 (d, 1H, J = 15.1 Hz), 4.57 (d, 1H, J = 15.1 Hz), 4.40 (t, 1H, J = 4.2 Hz), 3.49 (d, 2H, J = 4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.2, 171.2, 166.0, 162.6, 134.5, 133.2, 130.1, 129.1, 129.1, 129.0, 128.8, 128.6, 128.4, 128.2, 128.2, 126.7, 101.4, 59.4, 48.8, 26.9. Anal. Calcd for $C_{26}H_{21}N_3O_2S$: C, 71.04; H, 4.81; N, 9.56. Found: C, 70.68; H, 4.88; N, 9.46.

1-(4-Chlorophenyl)-3-[(3-phenylisoxazol-5-yl)methyl]-4-benzyl-5-thioxopyrrolidin-2-one (12l). Mp 197−198 °C; FTIR (KBr) 3127, 2932, 1752, 1613, 1494 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.73 (m, 2H), 7.59−7.37 (m, 10H), 7.17 (d, 2H, J = 8.5 Hz), 6.26 (s, 1H), 5.80 (d, 1H, J = 15.1 Hz), 4.58 (d, 1H, J = 15.1 Hz), 4.39 (t, 1H, J = 4.1 Hz), 3.48 (d, 2H, J = 4.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.7, 171.2, 165.9, 162.6, 135.2, 134.4, 131.6, 130.3, 129.6, 129.4, 129.2, 129.0, 128.6, 128.5, 128.4, 126.7, 101.6, 59.5, 49.0, 26.9. Anal. Calcd for $C_{26}H_{20}ClN_3O_2S$: C, 65.88; H, 4.25; N, 8.86. Found: C, 65.77; H, 4.26; N, 8.58.

4-[(3,4-Dimethoxyphenyl)methyl]-1-(3-chlorophenyl)-3-[(3-phenylisoxazol-5-yl)methyl]-5-thioxopyrrolidin-2-one (12n). Mp 176−177 °C; FTIR (KBr) 3111, 2931, 1747, 1593, 1464 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77−7.73 (m, 2H), 7.46−7.34 (m, 5H), 7.24 (m, 1H), 7.15−7.12 (m, 1H), 6.93−6.81 (m, 3H), 6.26 (s, 1H), 5.62 (d, 1H, J = 14.9 Hz), 4.58 (d, 1H, J = 14.9 Hz), 4.42 (t, 1H, J = 4.1 Hz), 3.86 (s, 3H), 3.81 (s, 3H), 3.48 (d, 2H, J = 4.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.3, 171.0, 166.0, 162.6, 149.4, 149.2, 134.5, 134.1, 130.2, 130.0, 129.4, 128.9, 128.6, 128.2, 126.9, 126.6, 126.6, 120.8, 111.6, 111.2, 101.5, 59.6, 55.9, 55.8, 48.9, 27.1. Anal. Calcd for $C_{28}H_{24}ClN_3O_4S$: C, 62.97; H, 4.53; N, 7.86. Found: C, 62.96; H, 4.53; N, 7.85.

4-[(3,4-Dimethoxyphenyl)methyl]-1-(4-chlorophenyl)-3-[(3-phenylisoxazol-5-yl)methyl]-5-thioxopyrrolidin-2-one (12o). Mp 172−173 °C; FTIR (KBr) 3111, 2947, 1746, 1616, 1478 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.72 (m, 2H), 7.47−7.40 (m, 5H), 7.19−7.16 (m, 2H), 6.95−6.82 (m, 3H), 6.25 (s, 1H), 5.63 (d, 1H, J = 15.0 Hz), 4.59 (d, 1H, J = 15.0 Hz), 4.42 (t, 1H, J = 4.4 Hz), 3.87 (s, 3H), 3.82 (s, 3H), 3.50 (d, 2H, J = 4.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.7, 171.2, 162.7, 160.1, 149.6, 149.4, 135.3, 131.6, 130.3, 129.6, 129.4, 129.0, 128.4, 127.0, 126.7, 120.9, 111.7, 111.3, 101.6, 59.7, 56.0, 55.9, 49.1, 27.2. Anal. Calcd for $C_{28}H_{24}ClN_3O_4S$: C, 62.97; H, 4.53; N, 7.86. Found: C, 62.87; H, 4.59; N, 7.84.

1-(3-Chlorophenyl)-3-[3-phenylisoxazol-5-yl)methyl]-4-(2-thienylmethyl)-5-thioxopyrrolidin-2-one (12q). Mp 160−161 °C; FTIR (KBr) 3045, 2906, 1754, 1612, 1480 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.74 (m, 2H), 7.47−7.30 (m, 6H), 7.21 (d, 1H, J = 2.3 Hz), 7.14−7.09 (m, 2H), 7.02−6.99 (m, 1H), 6.34 (s, 1H), 5.88 (d, 1H, J = 15.6 Hz), 4.75 (d, 1H, J = 15.6 Hz), 4.50 (t, 1H, J = 4.5 Hz), 3.56 (t, 2H, J = 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.0, 170.9, 166.0, 162.7, 136.1, 134.6, 134.0, 130.3, 130.0, 129.5, 129.0, 128.6, 128.4, 128.2, 127.1, 126.9, 126.8, 126.6, 101.6, 59.4, 43.5, 27.1. Anal. Calcd for $C_{24}H_{18}ClN_3O_2S_2$: C, 60.05; H, 3.78; N, 8.75. Found: C, 59.83; H, 3.85; N, 8.64.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and FTIR spectra for compounds **2**, **6**, **12d**, **12j**, **12l**, **12n**, **12o**, **12q**, **15**, **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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