Efficient Synthesis of Azaspirodienones by Microwave-Assisted Radical Spirocyclization of Xanthate-Containing Ugi Adducts

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Abstract: The sequential use of an Ugi reaction and radical spirocyclization under microwave irradiation conditions is described. The process provides rapid access to spirodienone lactams.

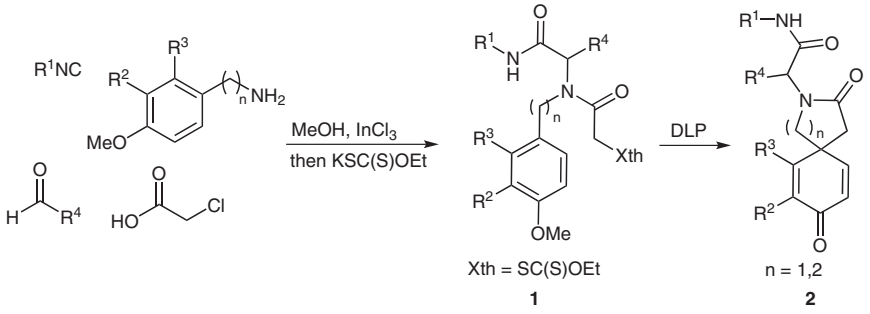
Key words: Ugi reaction, cyclizations, spiro compounds, lactams, microwave reactions

In medicinal chemistry, the screening of small-molecule libraries is of great importance in drug discovery. In this regard, an important goal in organic synthesis continues to be the development of efficient synthetic technologies that provide rapid access to libraries of molecules with broad structural diversity. Success in establishing an efficient combination of different reactions can lead to the assembly of libraries of small molecules (e.g., combinatorial chemistry). The selection of efficient consecutive processes does, indeed, merit consideration as a viable alternative means to create libraries of molecules bearing a variety of functional groups and having broad structural diversity.

We recently demonstrated that the sequential combination of an Ugi reaction with a free-radical cyclization leads to the efficient construction of different heterocyclic scaffolds.[1] Given that multicomponent reaction processes permit the rapid, convergent, and often efficient generation of small molecules,[2] and that radical processes have enormous utility in carbon–carbon bond-formation reactions,[3] we chose to study the possibility of the combination of these two reaction types. In this context, an efficient xanthate-based (cf. Zard et al.[4]) tin free-radical spirolactamization, involving the transformation of a benzenoid ring into a dienone system, was recently developed in our laboratory.[5] On the basis of this report, the utilization of a *p*-methoxybenzylamine derivative as the amine component in the Ugi reaction was expected to provide rapid access to substituted spirolactams, whose biological activity and complex structure make them an important synthetic target (Scheme 1).[6] The results of this endeavor are described herein. In a related nonradical approach, a one-pot entry to the synthesis of azaspirodienones by using a sequential combination of an Ugi reaction and a Michael cyclization was recently described by Santra and Andreana.[7]

Initially, the Ugi reaction was performed at room temperature in methanol, by using approximately equimolar amounts of the four components,[1] but the reactions were slow (10–20 h) under these conditions. When a catalytic amount of indium(III) chloride was added, the reactions were completed within a few hours. When the Ugi reaction was completed, the potassium salt of xanthic acid was added to the reaction mixture to generate the Ugi xanthate adducts, usually in excellent yields (Table 1).

With these materials in hand, we studied the spirocyclization reaction. The reported conditions involve the portionwise addition of lauroyl peroxide (DLP) over 12 hours to a boiling dichloroethane solution containing the Ugi xanthate adducts **1**.[5] These reactions were examined under microwave irradiation conditions to reduce the reaction time. Microwave-accelerated radical polymerization reac-



Scheme 1

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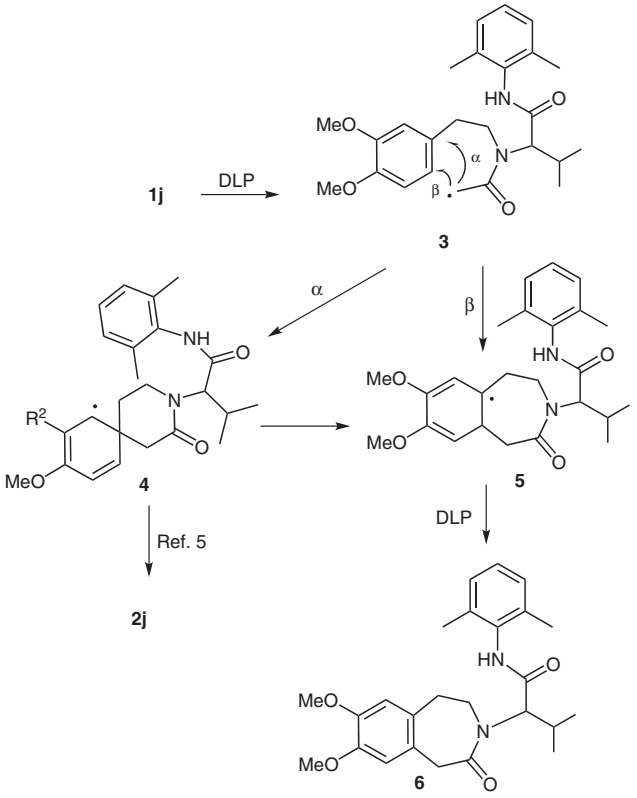
Table 1 Synthesis of Substituted Spirolactams **2**

Entry	R^1	R^2	R^3	R^4	n	Adduct **1**[a]	Yield (%)[b]	Spirodienone **2**[c]	Yield (%)[b]
1	2,6-$Me_2C_6H_3$	H	H	Et	1	**1a**	90	**2a**	82
2	2,6-$Me_2C_6H_3$	H	H	*i*-Pr	1	**1b**	98	**2b**	90
3	2,6-$Me_2C_6H_3$	H	H	4-ClC_6H_4	1	**1c**	93	**2c**	63
4	*t*-Bu	H	H	*i*-Pr	1	**1d**	95	**2d**	85
5	*t*-Bu	OMe	H	*i*-Pr	1	**1e**	93	**2e**	65
6	*t*-Bu	H	OMe	*i*-Pr	1	**1f**	97	**2f**	93
7	*t*-Bu	H	H	*i*-Pr	2	**1g**	98	**2g**	82
8	*t*-Bu	H	OMe	*i*-Pr	2	**1h**	85	**2h**	70
9	2,6-$Me_2C_6H_3$	H	H	*i*-Pr	2	**1i**	97	**2i**	93
10	2,6-$Me_2C_6H_3$	OMe	H	*i*-Pr	2	**1j**	97	**2j**	25

[a] Reaction conditions for the synthesis of the Ugi xanthate adducts **1**: amine, aldehyde, isocyanide, $ClCH_2CO_2H$, then KSC(S)OEt, $InCl_3$ (10 mmol%), MeOH (1 M), r.t.
[b] Isolated yield.
[c] Reaction conditions for the synthesis of the spirodienones **2**: Ugi xanthate adduct **1**, DLP (1.5 equiv, in 5 portions), toluene (0.1 M), 250 W, 100 °C, 25 min.

tions are now well documented,[8] but the use of this methodology in free-radical-based organic synthesis is less known.[9] Thus, the microwave-assisted radical spirocyclizations were performed in a monomodal open-vessel system.[10] The lauroyl peroxide (1.5 equiv) was added portionwise (0.3 equiv/5 min) to a microwave-irradiated (250 W, 100 °C) solution of the Ugi xanthate adduct in toluene, over a 25-minute period. Under these conditions, the product yields were similar to those obtained by the conventional method, but the reaction times were considerably shortened. Notable is that the portionwise addition of lauroyl peroxide (1.5 equiv) over 25 minutes to a solution of **1a** in toluene at 100 °C under conventional heating resulted in incomplete consumption of the starting material. A possible explanation is that the initiator fragmentation process and/or the radical propagation pathways are likely to be more efficient under microwave irradiation conditions.

The data in Table 1 show that functionalized five- and six-membered spirodienone lactams were obtained in good yields from both aliphatic and aromatic aldehydes in all cases but one. The dimethoxy-substituted Ugi adduct **1j** (entry 10) gave a mixture of the expected spirodienone **2j** (25% yield) and benzazepine **6** (45% yield) (Scheme 2) under conventional and microwave irradiation conditions. Compound **6** may arise by an initial *ipso* attack (Scheme 2, path α) and rearrangement of the spiro intermediate **4** to form a seven-membered radical precursor **5**, or by direct cyclization to this radical (Scheme 2, path β), or by a combination of both mechanisms. However, this is only a hypothesis at this point, because there is no experimental evidence for this intermediate.



Scheme 2 Proposed mechanism for the formation of **2j** and **6**

In closing, an efficient protocol for the preparation of substituted five- and six-membered spirolactams, by use of a sequential combination of an Ugi reaction and a microwave-assisted radical spirocyclization, was developed.

This protocol represents a very useful method for the construction of libraries of azaspirodienones.

All reactions were performed in anhydrous solvents under an argon atmosphere. General starting materials and solvents such as MeOH and toluene are commercially available and were acquired from Sigma Aldrich and used without further purification. The microwave-assisted radical spirocyclizations were performed by using a CEM Discover Synthesis™ Unit (CEM Corp., Matthews, NC) in a monomodal open-vessel system. Reaction progress was monitored by TLC on precoated Merck silica gel Kieselgel 60 F254 plates; the spots were visualized under UV light (254 nm). Flash chromatography was conducted on silica gel (230–400 mesh). Melting points were determined on a Fisher-Jones instrument. The IR spectra were measured on a NICOLET FT-55X spectrophotometer. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian Gemini 200, Varian Unity 300, and Bruker Avance 400 spectrometers. TMS was used as an internal reference. HRMS was carried out on a JEOL SX-102 instrument.

Ugi Reaction; General Procedure

A soln of the appropriate aldehyde (1.0 mmol), the appropriate amine (1.0 mmol), and $InCl_3$ (0.1 mmol) in anhyd MeOH (1 mL) was stirred for 1 h at r.t. Chloroacetic acid (1.0 mmol) was then added and the mixture was stirred for 15 min. The appropriate isocyanide (1.0 mmol) was then added and the reaction mixture was stirred for 2–4 h at r.t. until the reaction was completed (according to TLC). Then KSC(S)OEt (1.2 mmol) was added, and the mixture was stirred for 3 h. The mixture was filtered and the solvent was evaporated. The resulting residue was dissolved in EtOAc (5 mL). The organic layer was washed with distilled H_2O (3 × 7 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting yellowish solid was purified by column chromatography (silica gel, hexanes–EtOAc).

***S*-(*N*-{1-[*N*-(2,6-Dimethylphenyl)carbamoyl]propyl}-*N*-(4-methoxybenzyl)carbamoyl)methyl *O*-Ethyl Dithiocarbonate (1a)**

Yellow oil; R_f = 0.3 (hexanes–EtOAc, 8:2).

IR (film): 1650, 1589 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.0 Hz, 3 H), 1.37 (t, *J* = 7.0 Hz, 3 H), 1.85–1.90 (m, 1 H), 2.01–2.20 (m, 1 H), 2.16 (s, 6 H), 3.79 (s, 3 H), 4.05 (d, *J* = 16.0 Hz, 1 H), 4.10 (d, *J* = 16.0 Hz, 1 H), 4.61 (q, *J* = 7.0 Hz, 2 H), 4.77 (s, 2 H), 4.85–4.91 (m, 1 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 7.06 (m, 3 H), 7.25 (d, *J* = 8.8 Hz, 2 H), 7.91 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.0, 13.6, 18.5, 21.9, 39.8, 49.4, 55.2, 61.7, 70.7, 114.3, 127.1, 127.6, 128.1, 128.6, 133.6, 135.0, 159.1, 168.5, 169.3, 213.4.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{32}N_2O_4S_2$: 489.1882; found: 489.1877.

***S*-(*N*-{1-[*N*-(2,6-Dimethylphenyl)carbamoyl]-2-methylpropyl}-*N*-(4-methoxybenzyl)carbamoyl)methyl *O*-Ethyl Dithiocarbonate (1b)**

White solid; mp 139–140 °C; R_f = 0.3 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1640, 1513 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.4 Hz, 3 H,), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.40 (t, *J* = 7.0 Hz 3 H), 2.16 (s, 6 H), 2.62–2.75 (m, 1 H), 3.78 (s, 4 H), 3.97 (d, *J* = 16.0 Hz, 1 H), 4.23 (d, *J* = 16.0 Hz, 1 H), 4.63 (q, *J* = 7.2 Hz, 2 H), 4.73–4.75 (m, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 7.06 (m, 3 H), 7.26 (d, *J* = 8.6 Hz, 2 H), 8.18 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 13.9, 18.6, 19.9, 30.9, 40.0, 55.3, 70.8, 114.4, 127.1, 127.8, 128.1, 128.8, 133.8, 135.1, 159.2, 168.9, 169.4, 213.6.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{34}N_2O_4S_2$: 503.2038; found: 503.2036.

***S*-(*N*-{(4-Chlorophenyl)[*N*-(2,6-dimethylphenyl)carbamoyl]methyl}-*N*-(4-methoxybenzyl)carbamoyl)methyl *O*-Ethyl Dithiocarbonate (1c)**

White solid; mp 146–148 °C; R_f = 0.3 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1659, 1513 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 7.5 Hz, 3 H), 2.16 (s, 6 H), 3.76 (s, 3 H), 3.97 (d, *J* = 16.2 Hz, 1 H), 4.04 (d, *J* = 16.2 Hz, 1 H), 4.60 (q, *J* = 7.5 Hz, 2 H), 4.67 (d, *J* = 18.1 Hz, 2 H), 4.85 (d, *J* = 18.1 Hz, 2 H), 6.01 (br s, 1 H), 6.78 (d, *J* = 8.6 Hz, 2 H), 7.01–7.10 (m, 5 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.46 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 18.6, 39.9, 50.5, 55.3, 63.5, 70.6, 114.0, 127.4, 127.9, 128.2, 129.0, 131.2, 133.0, 133.2, 134.9, 135.4, 159.0, 167.3, 168.2, 213.9.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{31}ClN_2O_4S_2$: 571.1492; found: 571.1501.

***S*-{*N*-[1-(*N*-*tert*-Butylcarbamoyl)-2-methylpropyl]-*N*-(4-methoxybenzyl)carbamoyl}methyl *O*-Ethyl Dithiocarbonate (1d)**

White solid; mp 108–109 °C; R_f = 0.3 (hexanes–EtOAc, 8:2).

IR ($CHCl_3$): 1663, 1633 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.6 Hz, 3 H), 1.00 (d, *J* = 6.6 Hz, 3 H), 1.32 (s, 9 H), 1.42 (t, *J* = 8.0 Hz, 3 H), 2.33–2.40 (m, 1 H), 3.62 (d, *J* = 16.0 Hz, 1 H), 3.78 (s, 3 H), 4.10 (d, *J* = 16.0 Hz, 1 H), 4.32 (d, *J* = 11.0 Hz, 1 H), 4.62 (q, *J* = 8.0 Hz, 2 H), 4.68 (d, *J* = 16.8 Hz, 1 H), 4.93 (d, *J* = 16.8 Hz, 1 H), 6.28 (br s, 1 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 7.15 (d, *J* = 8.8 Hz, 2 H),

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 19.3, 19.8, 27.6, 28.8, 40.4, 51.5, 55.5, 70.7, 114.3, 128.1, 129.3, 159.1, 169.2, 169.4, 213.9.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{34}N_2O_4S_2$: 455.2038; found: 455.2043.

***S*-{*N*-[1-(*N*-*tert*-Butylcarbamoyl)-2-methylpropyl]-*N*-(3,4-dimethoxybenzyl)carbamoyl}methyl *O*-Ethyl Dithiocarbonate (1e)**

Yellow oil; R_f = 0.4 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1633, 1520 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.3 Hz, 3 H), 0.97 (d, *J* = 6.3 Hz, 3 H), 1.31 (s, 9 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 2.35–2.47 (m, 1 H), 3.78 (d, *J* = 16.0 Hz, 1 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.08 (d, *J* = 16.0 Hz, 1 H), 4.28 (d, *J* = 10.5 Hz, 1 H), 4.62 (q, *J* = 7.2 Hz, 2 H), 4.69 (d, *J* = 16.8 Hz, 1 H), 4.90 (d, *J* = 16.8 Hz, 1 H), 6.27 (br s, 1 H), 6.78–6.81 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 19.3, 19.6, 27.6, 28.6, 40.3, 51.3, 55.9, 56.0, 70.6, 110.3, 111.2, 118.9, 129.5, 148.4, 149.3, 169.1, 169.2, 213.8.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{37}N_2O_5S_2$: 485.2144; found: 485.2146.

***S*-{*N*-[1-(*N*-*tert*-Butylcarbamoyl)-2-methylpropyl]-*N*-(2,4-dimethoxybenzyl)carbamoyl}methyl *O*-Ethyl Dithiocarbonate (1f)**

Yellow oil; R_f = 0.37 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1642, 1622 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 1.28 (s, 9 H), 1.39 (t, *J* = 7.2 Hz, 3 H), 2.41–2.53 (m, 1 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 3.98 (d, *J* = 15.6 Hz, 1 H),

4.01–4.17 (m, 1 H), 4.21 (d, *J* = 15.6 Hz, 1 H), 4.59 (d, *J* = 17.0 Hz, 1 H), 4.61 (q, 2 H, *J* = 7.2 Hz), 4.72 (d, *J* = 17.0 Hz, 1 H), 6.41–6.43 (m, 2 H), 7.0 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 19.0, 19.7, 27.3, 28.6, 39.8, 51.0, 55.2, 55.3, 70.4, 98.4, 103.9, 116.9, 128.9, 157.8, 160.5, 168.9, 169.3, 213.7.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{36}N_2O_5S_2$: 484.2066; found: 484.2063.

S-{N-[1-(N-*tert*-Butylcarbamoyl)-2-methylpropyl]-N-(4-methoxyphenethyl)carbamoyl}methyl O-Ethyl Dithiocarbonate (1g)

White solid; mp 153–154 °C; R_f = 0.4 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1676, 1635 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 1.34 (s, 9 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 2.37–2.41 (m, 1 H), 2.81–3.00 (m, 2 H), 3.59–3.64 (m, 2 H), 3.79 (s, 3 H), 4.05 (d, *J* = 15.5 Hz, 1 H), 4.15 (d, *J* = 15.5 Hz, 1 H), 4.22 (m, 1 H), 4.64 (q, *J* = 7.2 Hz, 2 H), 6.33 (br s, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 7.17 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 18.7, 19.7, 26.5, 28.6, 35.0, 39.7, 51.2, 55.3, 70.7, 114.2, 129.9, 130.1, 158.5, 168.2, 169.5, 214.0.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{36}N_2O_4S_2$: 469.2195; found: 469.2186.

Xanthate **1h** was identified as its cyclized spirodienone **2h**.

S-(N-{1-[N-(2,6-Dimethylphenyl)carbamoyl]-2-methylpropyl}-N-(4-methoxyphenethyl)carbamoyl)methyl O-Ethyl Dithiocarbonate (1i)

White solid; mp 112–114 °C; R_f = 0.3 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1682, 1635 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.6 Hz, 3 H), 1.14 (d, *J* = 6.6 Hz, 3 H), 1.42 (t, *J* = 7.0 Hz, 3 H), 2.19 (s, 6 H), 2.69–2.71 (m, 1 H), 2.91–3.07 (m, 2 H), 3.60–3.74 (m, 3 H), 3.77 (s, 3 H), 4.22 (d, *J* = 15.5 Hz, 1 H), 4.29 (d, *J* = 15.5 Hz, 1 H), 4.66 (q, *J* = 7.0 Hz, 2 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 7.06 (m, 3 H), 7.15 (d, *J* = 8.4 Hz 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 18.7, 19.9, 35.1, 39.9, 55.2, 70.8, 114.2, 127.1, 128.2, 129.6, 129.8, 133.6, 134.9, 158.5, 168.7, 168.9, 213.7.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{36}N_2O_4S_2$: 517.2195; found: 517.2180.

S-(N-(3,4-Dimethoxyphenethyl)-N-{1-[N-(2,6-dimethylphenyl)carbamoyl]-2-methylpropyl}carbamoyl)methyl O-Ethyl Dithiocarbonate (1j)

White solid; mp 93–94 °C; R_f = 0.3 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1633, 1514 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.3 Hz 3 H), 1.15 (d, *J* = 6.3 Hz 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 2.18 (s, 6 H), 2.90–3.04 (m, 3 H), 3.64–3.77 (m, 2 H), 3.82–3.84 (m, 1 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 4.28 (br s, 2 H), 4.67 (q, *J* = 7.2 Hz, 2 H), 6.76 (s, 1 H), 6.79–6.80 (m, 2 H), 7.05–7.08 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 18.7, 19.9, 35.6, 40.2, 56.0, 70.9, 111.4, 112.0, 120.7, 127.2, 128.2, 130.1, 133.6, 134.9, 147.9, 149.1, 168.7, 213.8.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{39}N_2O_5S_2$: 547.2300; found: 547.2303.

Microwave-Assisted Radical Spirocyclization; General Procedure

A deaerated soln of the appropriate Ugi xanthate adduct (1 mmol) in anhyd toluene (5 mL) was microwave-irradiated (250 W) at 100 °C. Dilauryl peroxide (1.5 equiv) was then added portionwise (0.3 equiv/5min). The solvent was removed under reduced pressure and the residue was purified by chromatography (silica gel, hexanes–EtOAc); this furnished the corresponding spiro product.

Azaspiro[4.5]decane Derivative 2a

Yellow oil; R_f = 0.1 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1664, 1627 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.2 Hz, 3 H), 1.87–1.72 (m, 1 H), 2.00–2.17 (m, 1 H), 2.18 (s, 6 H), 2.57 (d, *J* = 17.0 Hz, 1 H), 2.64 (d, *J* = 17.0 Hz, 1 H), 3.49 (d, *J* = 10.5 Hz, 1 H), 3.80 (d, *J* = 10.5 Hz, 1 H), 4.72 (dd, *J* = 8.4, 7.5 Hz, 1 H), 6.28–6.31 (m, 2 H), 6.88–6.91 (m, 2 H), 6.94–7.06 (m, 3 H), 7.75 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.8, 18.5, 22.0, 41.2, 52.2, 57.2, 127.5, 128.2, 129.4, 129.5, 133.3, 135.0, 149.3, 149.5, 168.1, 172.5, 184.7.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}N_2O_3$: 353.1865; found: 353.1867.

Azaspiro[4.5]decane Derivative 2b

Yellow oil; R_f = 0.2 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1665, 1629 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.6 Hz, 3 H), 1.10 (d, *J* = 6.6 Hz, 3 H), 2.19 (s, 6 H), 2.20–2.39 (m, 1 H), 2.58 (d, *J* = 17.0 Hz, 1 H), 2.62 (d, *J* = 17.0 Hz, 1 H), 3.47 (d, *J* = 10. 6 Hz, 1 H), 3.82 (d, *J* = 10.6 Hz, 1 H), 4.38 (d, *J* = 11.0 Hz, 1 H), 6.28–6.30 (m, 2 H), 6.80 (dd, *J* = 10.0, 2.2 Hz, 1 H), 6.97 (dd, *J* = 10.0, 2.2 Hz, 1 H), 7.05–7.07 (m, 3 H), 7.78 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 19.2, 19.7, 26.5, 41.3, 51.9, 62.7, 127.7, 128.4, 129.5, 130.0, 133.5, 135.0, 149.5, 149.7, 167.4, 172.8, 184.9.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{27}N_2O_3$: 367.2022; found: 367.2025.

Azaspiro[4.5]decane Derivative 2c

White solid; mp 170–172 °C; R_f = 0.3 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1660, 1628, 1594 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15 (s, 6 H), 2.58 (s, 2 H), 3.10 (d, *J* = 9.9 Hz, 1 H), 3.90 (d, *J* = 9.9 Hz, 1 H), 6.11 (s, 1 H), 6.22 (dt, *J* = 9.6, 1.8 Hz, 2 H), 6.70 (m, 1 H), 7.02–7.12 (m, 4 H), 7.38 (s, 1 H), 7.43 (br s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 40.9, 41.5, 52.3, 58.3, 127.8, 128.3, 128.9, 129.6, 130.5, 132.0, 132.8, 135.3, 135.6, 149.2, 150.0, 167.1, 171.9, 184.8.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{23}ClN_2O_3$: 435.1475; found: 435.1480

Azaspiro[4.5]decane Derivative 2d

Colorless oil; R_f = 0.2 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1664, 1629 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 1.35 (s, 9 H), 2.20 (m, 1 H), 2.55 (d, *J* = 16.8 Hz, 1 H), 2.63 (d, *J* = 16.8 Hz, 1 H), 3.44 (d, *J* = 10.5 Hz, 1 H), 3.78 (d, *J* = 11.0 Hz, 1 H), 3.96 (d, *J* = 11.0 Hz, 1 H), 5.90 (br s, 1 H), 6.31 (dd, *J* = 10.2, 1.8 Hz, 1 H), 6.33 (dd, *J* = 10.2, 1.8 Hz, 1 H), 6.85 (dd, *J* = 10.0, 3.0 Hz, 1 H), 6.93 (dd, *J* = 10.2, 3.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 19.3, 26.7, 28.6, 41.2, 41.4, 51.7, 63.0, 129.5, 149.4, 149.5, 168.0, 172.2, 184.8.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{18}H_{27}N_2O_3$: 319.2022; found: 319.2025.

Azaspiro[4.5]decane Derivative 2e
Inseparable mixture of diastereomers (~6:4); R_f = 0.3 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1667, 1616 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (1st diastereomer) = 0.93 (dd, *J* = 6.6, 5.1 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 1.36 (s, 9 H), 2.21 (m, 1 H), 2.57 (d, *J* = 17.0 Hz, 1 H), 2.67 (d, *J* = 17.0 Hz, 1 H), 3.47 (d, *J* = 10.0 Hz, 1 H), 3.66 (s, 3 H), 3.82 (d, *J* = 10.5 Hz, 1 H), 3.96 (d, *J* = 11.0 Hz, 1 H), 5.80 (br s, 1 H), 5.82 (d, *J* = 2.7 Hz, 1 H), 6.36 (d, *J* = 9.6 Hz, 1 H), 6.94 (dd, *J* = 9.6, 2.4 Hz, 1 H).

^{1}H NMR (300 MHz, $CDCl_3$): δ (2nd diastereomer) = 0.93 (dd, *J* = 6.6, 5.1 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 1.35 (s, 9 H), 1.71 (br s, 1 H), 2.21 (m, 1 H), 2,59 (d, *J* = 17.0 Hz, 1 H), 2.66 (d, *J* = 17.0 Hz, 1 H), 3.44 (d, *J* = 10.0 Hz, 1 H), 3.68 (s, 3 H), 3.80 (d, *J* = 10.5 Hz, 1 H), 3.91 (d, *J* = 11.0 Hz, 1 H), 5.75 (d, *J* = 2.7 Hz, 1 H), 6.34 (d, *J* = 9.6 Hz, 1 H), 6.84 (dd, *J* = 9.6, 2.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 19.4, 26.7, 28.6, 42.2, 42.3, 51.7, 52.8, 54.9, 63.0, 116.8, 128.9, 149.8, 151.7, 168.3, 172.6, 180.1.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{19}H_{28}N_2O_4$: 349.2127; found: 349.2118.

Azaspiro[4.5]decane Derivative 2f
Inseparable mixture of diastereomers (~7:3); R_f = 0.3 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1661, 1626 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (1st diastereomer) = 0.91 (dd, *J* = 6.9, 6.6 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.35 (s, 9 H), 2.21 (m, 1 H), 2.44 (d, *J* = 17.0 Hz, 1 H), 2.95 (d, *J* = 17.0 Hz, 1 H), 3.68 (s, 2 H), 3.79 (s, 3 H), 3.96 (d, *J* = 11.1 Hz, 1 H), 5.64 (s, 1 H), 5.78 (br s, 1 H), 6.18 (dd, *J* = 10.0, 1.5 Hz, 1 H), 6.59 (d, 1 H, *J* = 10.0 Hz).

^{1}H NMR (300 MHz, $CDCl_3$): δ (2nd diastereomer) = 0.91 (dd, *J* = 6.9, 6.6 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.35 (s, 9 H), 2.21 (m, 1 H), 2.43 (d, *J* = 17.0 Hz, 1 H), 2.90 (d, *J* = 17.0 Hz, 1 H), 3.30 (d, *J* = 11.0 Hz, 1 H), 3.75 (s, 3 H), 3.90 (d, *J* = 10.0 Hz, 1 H), 3.93 (d, *J* = 11.0 Hz, 1 H), 5.85 (br s, 1 H), 6.21 (dd, *J* = 9.6, 1.5 Hz, 1 H), 6.70 (d, 1 H, *J* = 10.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3, 19.8, 27.3, 29.0, 40.9, 42.4, 52.0, 52.2, 56.5, 63.4, 103.4, 127.5, 146.7, 168.6, 172.4, 174.7, 187.4.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{19}H_{28}N_2O_4$: 348.2049; found: 348.2058.

Azaspiro[5.5]undecane Derivative 2g
R_f = 0.4 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1667, 1635 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.5 Hz, 3 H), 1.01 (d, *J* = 6.5 Hz, 3 H), 1.35 (s, 9 H), 1.94 (m, 2 H), 2.34 (m, 1 H), 2.43 (dd, *J* = 17.0, 0.9 Hz, 1 H), 2.55 (d, *J* = 17.0 Hz, 1 H), 3.41–3.49 (m, 1 H), 3.75 (ddd, *J* = 13.5, 7.8, 6.0 Hz, 1 H), 4.49 (d, *J* = 11.0 Hz, 1 H), 6.00 (br s, 1 H), 6.29–6.35 (m, 2 H), 6.77 (dd, *J* = 10.0, 3.6 Hz, 1 H), 6.83 (dd, *J* = 10.0, 3.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 19.6, 25.3, 28.7, 32.4, 39.1, 40.0, 40.6, 51.4, 63.4, 129.6, 150.2, 150.8, 167.8, 168.5, 184.8.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{23}H_{29}N_2O_3$: 333.2178; found: 333.2180.

Azaspiro[5.5]undecane Derivative 2h
White solid; mp 156–158 °C; R_f = 0.2 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1660, 1593 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.6 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 1.35 (s, 9 H), 1.80 (m, 1 H), 2.24 (d, *J* = 16.5 Hz, 1 H), 2.25 (m, 2 H), 2.97 (d, *J* = 16.5 Hz, 1 H), 3.51–3.43 (m, 1 H), 3.64 (ddd, *J* = 14.0, 9.6, 5.1 Hz, 1 H), 3.77 (s, 1 H), 4.47 (d, *J* = 11.0 Hz, 1 H), 5.60 (d, *J* = 1.5 Hz, 1 H), 5.96 (br s, 1 H), 6.20 (dd, *J* = 10.0, 1.5 Hz, 1 H), 6.54 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 19.6, 25.5, 28.7, 31.8, 39.4, 39.9, 51. 4, 56,0, 63.2, 102.3, 128.0, 146.1, 168.61, 169.0, 186.8.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{20}H_{30}N_2O_4$: 363.2284; found: 363.2283.

Azaspiro[5.5]undecane Derivative 2i
R_f = 0.4 (hexanes–EtOAc, 7:3).

IR (film): 1654, 1629 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.6 Hz, 3 H), 1.14 (d, *J* = 6.6 Hz, 3 H), 1.95 (m, 2 H), 2.20 (s, 6 H), 2.45 (m, 1 H), 2.47 (d, *J* = 17.0 Hz, 1 H), 2.58 (d, *J* = 17.0 Hz, 1 H), 3.52 (ddd, *J* = 13.5, 7.2, 6.3 Hz, 1 H), 3.83–3.75 (m, 1 H), 4.83 (d, *J* = 11.0 Hz, 1 H), 6.31 (dd, *J* = 10.0, 1.8 Hz, 1 H,), 6.36 (dd, *J* = 10.0, 1.8 Hz, 1 H), 6.78 (dd, *J* = 10.0, 3.0 Hz, 1 H), 6.90 (dd, *J* = 10.0, 3.0 Hz, 1 H), 7.09–7.05 (m, 3 H), 7.65 (br s, 1 H),

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 19.0, 19.7, 25.2, 32.6, 40.7, 63.6, 127.4, 128.3, 129.6, 129.9, 133.5, 134.8, 149.9, 150.6, 167.7, 168.1, 184.7,

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{23}H_{29}N_2O_3$: 381.2178; found: 381.2179.

Azaspiro[5.5]undecane Derivative 2j
Inseparable mixture of diastereomers (~1:1); white solid; mp 123–124 °C; R_f = 0.2 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1672, 1641, 1625 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (1st diastereomer) = 1.01 (dd, *J* = 3.3, 6.5 Hz, 3 H), 1.14 (d, *J* = 6.5 Hz, 3 H), 1.95 (m, 2 H), 2.21 (s, 6 H), 2.51 (d, *J* = 17.1 Hz, 1 H), 2.57 (s, 1 H), 2.63 (d, *J* = 17.1, 1.2 Hz, 1 H), 3.42–3.60 (m, 1 H), 3.67 (s, 3 H), 3.74–3.85 (m, 2 H), 4.80 (m, 1 H), 5.79 (d, *J* = 2.7 Hz, 1 H), 6.39 (d, *J* = 10.0 Hz, 1 H), 6.90 (dd, *J* = 10.0, 3.0 Hz, 1 H), 7.04–7.12 (m, 3 H), 7.64 (br s, 1 H).

^{1}H NMR (300 MHz, $CDCl_3$): δ (2nd diastereomer) = 1.02 (dd, *J* = 3.3, 6.5 Hz, 3 H), 1.14 (d, *J* = 6.5 Hz, 3 H), 1.95 (m, 2 H), 2.20 (s, 6 H), 2.4 (m, 1 H), 2.51 (d, *J* = 17.1 Hz, 1 H), 2.63 (d, *J* = 17.1, 1.2 Hz, 1 H), 3.49–3.59 (m, 1 H), 3.62 (m, 3 H), 3.74–3.85 (m, 1 H), 4.80 (m, 1 H), 5.64 (d, *J* = 2.7 Hz, 1 H), 6.35 (d, *J* = 10.0 Hz, 1 H), 6.79 (dd, *J* = 10.0, 3.0 Hz, 1 H), 7.04–7.12 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 18.8, 19.1, 19.7, 25.2, 33.4, 33.6, 39.6, 41.9, 55.0, 63.0, 116.5, 117.7, 127.4, 128.3, 128.9, 129.2, 133.4, 134.8, 150.4, 151.1, 151.9, 167.7, 168.4, 180.1.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{24}H_{30}N_2O_4$: 411.2284; found: 411.2281.

Benzazepine 6
Yield: 45%; white solid; mp 172–173 °C; R_f = 0.7 (hexanes–EtOAc, 7:3).

IR ($CHCl_3$): 1633 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.6 Hz, 3 H), 1.10 (d, *J* = 6.6 Hz, 3 H), 1.90 (s, 6 H), 2.52–2.50 (m, 1 H), 2.91–3.00 (m, 1 H), 3.15–3.04 (m, 1 H), 3.59 (d, *J* = 14.4 Hz, 1 H), 3.79 (s, 3 H), 3.85 (s, 3 H), 3.80–3.85 (m, 1 H), 3.94–4.04 (m, 1 H), 4.20 (d, *J* = 14.4 Hz, 1 H), 4.68 (br s, 1 H), 6.48 (s, 1 H), 6.60 (s, 1 H), 6.93–7.05 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9, 18.7, 19.7, 25.8, 32.0, 42.3, 55.9, 113.2, 113.8, 122.3, 127.1, 128.0, 133.5, 134.9, 147.2, 148.2, 168.9, 173.7.

HRMS–FAB: *m/z* [M + H]$^+$ calcd for $C_{25}H_{32}N_2O_4$: 424.2362; found: 424.2371.

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