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Synthesis of Spirodienones by Intramolecular Ipso-Cyclization of *N*-Methoxy-(4-halogenophenyl)amides Using [Hydroxy(tosyloxy)iodo]benzene in Trifluoroethanol

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Abstract: Spirodienones bearing the 1-azaspiro[4.5]decane ring system have been synthesized from *N*-methoxy-(4-halogenophenyl)amides by the intramolecular ipso attack of a nitrenium ion generated with [hydroxy(tosyloxy)iodo]-benzene in trifluoroethanol.

TAN1251A-D,[1] FR901483,[2] lepadiformine,[3] and cylindricine[4] isolated by Takeda Industries, by Fujisawa Pharmaceutical Co., by Biard and co-workers, and by Blackman and co-workers, respectively, are architecturally interesting natural products which have a novel 1-azaspiro[4.5]decane skeleton (Figure 1). Construction of the 1-azaspiro[4.5]decane skeleton has been achieved by oxidative spirocyclizations of phenolic oxazolines,[5] of phenolic sulfonamides,[6] and of *N*-methoxyamides[7] via *N*-methoxy-*N*-acylnitrenium ion intermediates using hypervalent iodine compounds.

The last method has been the subject of our own research. In this earlier work, we developed procedures for the synthesis of the 1-azaspiro[4.5]decane skeleton by intramolecular ipso attack of a nitrenium ion generated from an *N*-chloro-*N*-methoxyamide moiety appended to the 4-methoxybenzene substrate.[8] It is generally accepted that the spirodienones are the major or the exclusive products whenever the aromatic ring bears a methoxy group para to the alkyl side chain (Table 1).[7−10] This is a very useful transformation since the spiro compounds so generated have proved to be valuable intermediates for the synthesis of biologically important compounds. To make the process even more versatile, we have investigated the synthesis of substituted spirodienones by this strategy using more readily accessible starting compounds.

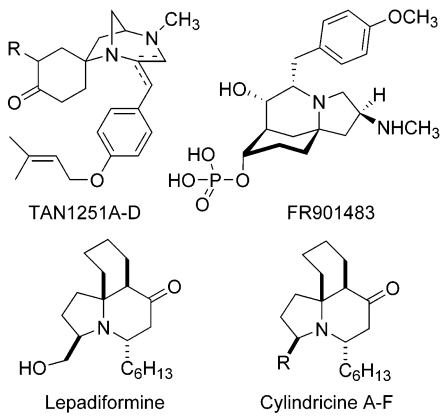
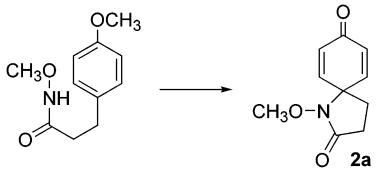


FIGURE 1. Natural products bearing 1-azaspiro[4.5]decane skeleton.

TABLE 1. Synthesis of 1-Methoxy-1-azaspiro[4.5]decadienone (2a) Hitherto Reported



entry	conditions	yield (%)
1	(1) *t*-BuOCl (2) Ag_2CO_3/TFA, ice cooling	83[a]
2	PIFA/CH_2Cl_2, CH_3OH, 0 °C	72[b]
3	PIFA/TFEA, ice cooling	80[c]

[a] Reference 8. [b] Reference 7a. [c] Reference 10.

Because 4-halogenophenyl compounds are more readily accessible than the corresponding methoxy compounds, we have examined the synthesis of spirodienones using *N*-methoxy-(4-halogenophenyl)amides (**1**) with hypervalent iodine compounds. Hypervalent iodine compounds have low toxicity, are readily available, are easy to handle, and are environmentally friendly.

The following experiment exemplifies the successful outcome of these efforts. To 3-(4-fluorophenyl)-*N*-methoxypropionamide (**1a**) (0.5 mmol) in trifluoroethanol (TFEA) (5 mL) was added [hydroxy(tosyloxy)iodo]benzene (HTIB) (1.0 mmol) portionwise over 10 min. The solution was stirred for 5 min with ice cooling. After usual workup, 1-methoxy-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (**2a**) was obtained in 82% yield.

Several halogeno compounds (**1**) reacted in this way, and the results are presented in Table 2. Generally fluorine-substituted starting compounds give good results. Reactions of **1e** and **1f** gave the corresponding spirobenzannulated compounds (**2e** and **2f**) and a complex mixture of benzannulated compounds in which compound **3** could be isolated by careful column chromatography (Table 2, entry 5).

(1) Shirafuji, H.; Tsubotani, S.; Ishimaru, T.; Harada, S. Int. Patent PCT, WO91/13887, 1991.
(2) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37.
(3) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691.
(4) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645.
(5) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534.
(6) Canesi, S.; Belmont, P.; Bouchu, D.; Rousset, L.; Ciufolini, M. A. *Tetrahedron Lett.* **2002**, *43*, 5193.
(7) (a) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353. (b) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053.
(8) Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394.
(9) Glover, S. A.; Goosen, A.; McCleland, C. W.; Schoonraad, J. L. *Tetrahedron* **1987**, *43*, 2577.
(10) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *Heterocycles* **2003**, *59*, 149.

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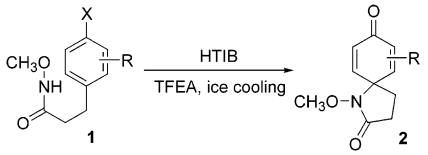
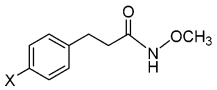
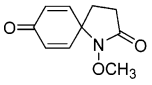
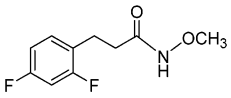
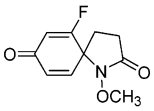
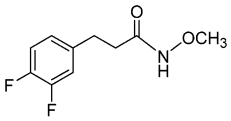
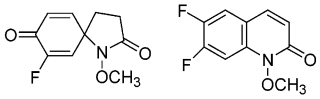
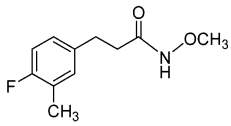
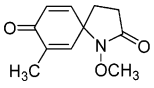
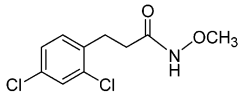
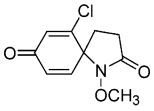
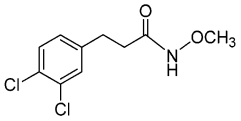
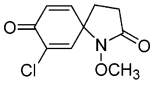
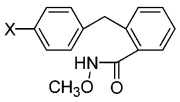
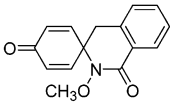
TABLE 2. Synthesis of Spirodienones from *N*-Methoxy-(4-halogenophenyl)amides with HTIB in TFEA



1 **2**

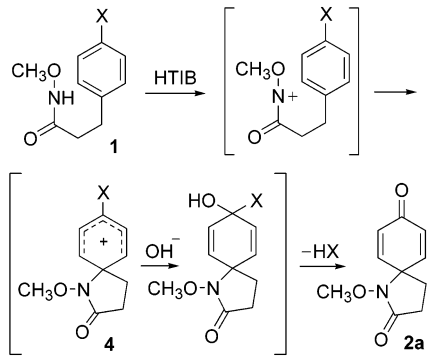
entry	starting material		time (min)	product yield (%)
1		**1a**: X = F	5	 **2a** (82)
2		**1b**: X = Cl	60	**2b** (72)
3		**1c**: X = Br	60	**2c** (62)
4		**1d**	5	 **2d** (65)
5		**1e**	5	 **2e** (37) **3** (14)
6		**1f**	5	 **2f** (66)
7		**1g**	60	 **2g** (38)
8		**1h**	60	 **2h** (28)
9		**1i**: X = F	5	 **2i** (88)
10		**1j**: X = Cl	60	**2j** (80)

Two equivalents of HTIB to **1b** were needed to obtain a high yield of **2b**, and the starting compound was recovered by use of 1.1 equiv of HTIB in 1 h (23%). Use of phenyliodine(III) bis(trifluoroacetate) (PIFA) (2 equiv) instead of HTIB gave **2b** in low yield (54%). As for solvents TFEA, $(CF_3)_2CHOH$, $CHF_2CF_2CH_2OH$, and CF_3-COOH were suitable; among them TFEA is the solvent of choice, while spirodienones were obtained in poor yields using CH_3CN and $CHCl_3$. The reaction proceeds through a cationic intermediate by the intramolecular ipso attack of a nitrenium ion.[11]

A proposed mechanism is illustrated in Scheme 1.

Principally, the spirodienones are obtained whenever the aromatic ring bears a highly electron-donating methoxy group para to the alkyl side chain.[7−10] However, the influence of para substitution by halogen atoms on the phenyl ring is of particular interest in view of the opposing inductive and conjugative effects. Halogens are considered to be electron-withdrawing groups due to their electronegativity but at the same time they also have nonbonded electron pairs, which stabilize the intermediate (**4**) through their "back-donation" ability and promote

SCHEME 1



1 **4** **2a**

further reaction.[12] The degree of "back-donation" corresponds to the yields of spirodienones and the best results are obtained in the case of fluorine (Table 2, entry 9).

In conclusion, **2** bearing the 1-azaspiro[4.5]decane ring system have been synthesized from *N*-methoxy-(4-halogenophenyl)amides with HTIB in TFEA probably because

(11) Glover, S. A.; Rowbottom, C. A.; Scott, A. P.; Schoonraad, J. L. *Tetrahedron* **1990**, *46*, 7247.

(12) Olah, G. A.; Singh, B. P.; Liang, G. *J. Org. Chem.* **1984**, *49*, 2922; Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 2* **1998**, 7.

a halogen atom has a cation stabilizing effect and is a good leaving group. These spirodienones, themselves of potential synthetic interest, can be converted into 7-oxygenated quinolone derivatives in acidic conditions through the dienone−phenol rearrangement.[13]

Experimental Section

General Methods. Melting points are uncorrected. NMR spectra were recorded at 270 MHz (^{1}H) and 68 MHz (^{13}C) with TMS as the internal reference. Mass spectra were measured with direct inlet system at 70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this University.

Materials. Compounds **1a**,**b**,**d**,**e** were prepared by the Schotten−Baumann reaction of the corresponding carboxylic acid chlorides with methoxyamine hydrochloride in diethyl ether−H_2O.[8] These carboxylic acids, except for commercially available 3,4-difluorophenylpropionic acid, were prepared by catalytic hydrogenation (Pd/C) of the corresponding cinnamic acid derivatives. Compounds **1c**,**g**,**h** were prepared by catalytic hydrogenation (Pd/C) of the corresponding *N*-methoxycinnamamides, which were synthesized by the Schotten−Baumann reaction of the corresponding cinnamic acid chlorides with methoxyamine hydrochloride in diethyl ether−H_2O. Compound **1f** was prepared similarly from 3-methyl-4-fluorocinnamic acid which was synthesized from 2-fluoro-3-methylbenzaldehyde with malonic acid in pyridine.[14] Compounds **1i** and **1j** were prepared similarly from the corresponding acids which were synthesized from the corresponding ketones by Zn−NH_4OH reduction.[15]

3-(4-Fluorophenyl)-*N*-methoxypropionamide (1a): white crystals; mp 55.5−56 °C (AcOEt/hexane); IR (KBr) 3150, 1650, 1510, 1220, 1070 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.23 (t, J = 7.5 Hz, 2H), 2.81 (t, J = 7.5 Hz, 2H), 3.53 (s, 3H), 7.09 (t, $J_{H-F=H-H}$ = 8.9 Hz, 2H), 7.22 (dd, J_{H-H} = 7.6 Hz, J_{H-F} = 6.1 Hz, 2H), 10.96 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.8, 34.0, 63.0, 114.8 (d, J_{C-F} = 21.2 Hz), 129.9 (d, J_{C-F} = 7.8 Hz), 136.7 (d, J_{C-F} = 2.8 Hz), 160.5 (d, J_{C-F} = 240.4 Hz), 167.8; EI-MS *m*/*z* 197 (M$^+$, 24.7), 151 (25.9), 123 (28.4), 109 (100). Anal. Calcd for $C_{10}H_{12}NO_2F$: C, 60.91; H, 6.13; N, 7.10. Found: C, 60.80; H, 6.12; N, 7.07.

3-(4-Chlorophenyl)-*N*-methoxypropionamide (1b): white crystals; mp 73−75 °C (Et_2O/petroleum ether); IR (KBr) 3250, 1660, 1520, 1495, 1100 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.23 (t, J = 7.5 Hz, 2H), 2.80 (t, J = 7.5 Hz, 2H), 3.52 (s, 3H), 7.22 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 10.96 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.9, 33.7, 63.1, 128.1, 130.0, 130.4, 139.7, 167.7; EI-MS *m*/*z* 215 (M$^+$ + 2, 10.8), 213 (M$^+$, 32.8), 167 (25.7), 139 (38.3), 125 (100). Anal. Calcd for $C_{10}H_{12}NO_2Cl$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.05; H, 5.62; N, 6.48.

3-(4-Bromophenyl)-*N*-methoxypropionamide (1c): white crystals; mp 82−85 °C (Et_2O); IR (KBr) 3240, 1655, 1520, 1490, 1075 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.23 (t, J = 7.4 Hz, 2H), 2.79 (t, J = 7.4 Hz, 2H), 3.53 (s, 3H), 7.16 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 7.8 Hz, 2H), 10.97 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 30.0, 33.6, 63.1, 118.9, 130.4, 130.9, 140.1, 163.7; EI-MS *m*/*z* 259 (M$^+$ + 2, 33.5), 257 (M$^+$, 34.1), 211 (37.2), 185 (38.6), 169 (100), 104 (38.7). Anal. Calcd for $C_{10}H_{12}NO_2Br$: C, 46.53; H, 4.69; N, 5.43. Found: C, 46.64; H, 4.54; N, 5.34.

3-(2,4-Difluorophenyl)-*N*-methoxypropionamide (1d): white crystals; mp 82−83 °C (Et_2O); IR (KBr) 3150, 1660, 1500, 1095 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.24 (t, J = 7.6 Hz, 2H), 2.83 (t, J = 7.6 Hz, 2H), 3.53 (s, 3H), 7.01 (td, $J_{H-F=H-H}$ = 8.1, 2.4 Hz, 1H), 7.17 (td, J_{H-F} = 9.9 Hz, J_{H-H} = 2.4 Hz, 1H), 7.31 (q, $J_{H-F=H-H}$ = 8.1 Hz, 1H), 11.02 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.6 (d, J_{C-F} = 1.9 Hz), 32.4, 63.1, 103.5 (t, J_{C-F} = 25.9 Hz), 111.1 (dd, J_{C-F} = 20.6, 3.3 Hz), 123.4 (dd, J_{C-F} = 16.1, 3.6 Hz), 131.5 (dd, J_{C-F} = 9.7, 6.4 Hz), 160.1 (dd, J_{C-F} = 211.3, 12.0 Hz), 160.7 (dd, J_{C-F} = 227.8, 12.0 Hz), 167.6; EI-MS *m*/*z* 215 (M$^+$, 22.3), 169 (34.0), 141 (38.0), 127 (100). Anal. Calcd for $C_{10}H_{11}NO_2F_2$: C, 55.81; H, 5.15; N, 6.51. Found: C, 55.73; H, 5.14; N, 6.44.

3-(3,4-Difluorophenyl)-*N*-methoxypropionamide (1e): white crystals; mp 81−82 °C (Et_2O); IR (KBr) 3230, 1660, 1520, 1280 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.26 (t, J = 7.5 Hz, 2H), 2.82 (t, J = 7.5 Hz, 2H), 3.53 (s, 3H), 6.98−7.13 (m, 1H), 7.20−7.40 (m, 2H), 10.99 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.7, 33.5, 63.1, 117.0 (dd, J_{C-F} = 16.2, 5.0 Hz), 124.9 (dd, J_{C-F} = 6.1, 3.3 Hz), 138.4 (dd, J_{C-F} = 5.9, 3.2 Hz), 147.4 (dd, J_{C-F} = 242.4, 12.5 Hz), 148.9 (dd, J_{C-F} = 243.9, 12.8 Hz), 167.7; EI-MS *m*/*z* 215 (M$^+$, 35.7), 169 (34.0), 141 (58.4), 127 (100). Anal. Calcd for $C_{10}H_{11}NO_2F_2$: C, 55.81; H, 5.15; N, 6.51. Found: C, 55.74; H, 5.12; N, 6.49.

3-(4-Fluoro-3-methylphenyl)-*N*-methoxypropionamide (1f): white crystals; mp 58−59 °C (AcOEt/hexane); IR (KBr) 3230, 1660, 1515, 1210 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.16−2.26 (m, 5H), 2.75 (t, J = 7.6 Hz, 2H), 3.52 (s, 3H), 6.98−7.14 (m, 3H), 10.95 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.2 (d, J_{C-F} = 3.3 Hz), 29.8, 34.0, 63.0, 114.4 (d, J_{C-F} = 21.8 Hz), 123.5 (d, J_{C-F} = 17.3 Hz), 127.8 (d, J_{C-F} = 7.8 Hz), 132.0 (d, J_{C-F} = 4.5 Hz), 136.4, 159.0 (d, J_{C-F} = 239.9 Hz), 167.8; EI-MS *m*/*z* 211 (M$^+$, 20.2), 165 (14.7), 137 (18.8), 123 (100). Anal. Calcd for $C_{11}H_{14}NO_2F$: C, 62.55; H, 6.68; N, 6.63. Found: C, 62.44; H, 6.64; N, 6.59.

3-(2,4-Dichlorophenyl)-*N*-methoxypropionamide (1g): white crystals; mp 59.5−60 °C (AcOEt/hexane); IR (KB) 3170, 1650, 1540, 1480, 1080, 1050 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.26 (t, J = 7.6 Hz, 2H), 2.91 (t, J = 7.6 Hz, 2H), 3.54 (s, 3H), 7.28−7.42 (m, 2H), 7.57 (s, 1H), 11.02 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.9, 31.7, 63.1, 127.2, 128.4, 131.5, 131.7, 133.6, 137.1, 167.4; EI-MS *m*/*z* 251 (M$^+$ + 4, 0.31), 249 (M$^+$ + 2, 0.68), 247 (M$^+$, 0.50), 212 (51.4), 173 (51.0), 159 (100); FAB-MS (matrix NBA) *m*/*z* 248 (M$^+$ + 1, 100). Anal. Calcd for $C_{10}H_{11}NO_2Cl_2$: C, 48.41; H, 4.47; N, 5.65. Found: C, 48.45; H, 4.45; N, 5.66.

3-(3,4-Dichlorophenyl)-*N*-methoxypropionamide (1h): white crystals; mp 97−98 °C (Et_2O); IR (KBr) 3240, 1660, 1525, 1475, 1140 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.26 (t, J = 7.3 Hz, 2H), 2.82 (t, J = 7.3 Hz, 2H), 3.53 (s, 3H), 7.20 (d, J = 8.0 Hz, 1H), 7.47 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 10.97 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.4, 33.1, 62.9, 128.3, 128.5, 130.0, 130.1, 130.4, 141.8, 167.4; EI-MS *m*/*z* 251 (M$^+$ + 4, 3.8), 249 (M$^+$ + 2, 22.4), 247 (M$^+$, 35.4), 201 (28.8), 173 (56.1), 159 (100). Anal. Calcd for $C_{10}H_{11}NO_2Cl_2$: C, 48.41; H, 4.47; N, 5.65. Found: C, 48.45; H, 4.51; N, 5.44.

2-(4-Fluorobenzyl)-*N*-methoxybenzamide (1i): white crystals; mp 115−115.5 °C (AcOEt/hexane); IR (KBr) 3140, 1640, 1520, 1235, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H), 4.12 (s, 2H), 6.92 (t, $J_{H-F=H-H}$ = 8.8 Hz, 2H), 7.11 (dd, J_{H-H} = 8.6 Hz, J_{H-F} = 5.4 Hz, 2H), 7.17−7.27 (m, 2H), 7.28−7.42 (m, 2H), 8.55 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 37.9, 64.4, 115.0 (d, J_{C-F} = 21.2 Hz), 126.3, 127.4, 130.3 (d, J_{C-F} = 7.9 Hz), 130.7, 130.9, 132.4, 136.0 (d, J_{C-F} = 3.3 Hz), 139.8, 161.2 (d, J_{C-F} = 243.8 Hz), 167.4; EI-MS *m*/*z* 259 (M$^+$, 7.3), 227 (17.7), 213 (100), 183 (31.6). Anal. Calcd for $C_{15}H_{14}NO_2F$: C, 69.49; H, 5.44; N, 5.40. Found: C, 69.56; H, 5.37; N, 5.32.

2-(4-Chlorobenzyl)-*N*-methoxybenzamide (1j): white crystals; mp 111−112 °C (AcOEt); IR (KBr) 3140, 1640, 1500, 1325, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H), 4.12 (s, 2H), 7.08 (d, J = 8.6 Hz, 2H), 7.15−7.45 (m, 6H), 8.60 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 38.0, 64.4, 126.4, 127.4, 128.3, 130.3, 130.8, 130.9, 131.8, 132.4, 138.8, 139.5, 167.4; EI-MS *m*/*z* 277 (M$^+$ + 2, 3.5), 275 (M$^+$, 10.2), 244 (22.3), 229 (100), 194 (66.5), 165 (43.9). Anal. Calcd for $C_{15}H_{14}NO_2Cl$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.55; H, 5.15; N, 5.08.

Reaction of 3-(4-Fluorophenyl)-*N*-methoxypropionamide (1a) with HTIB in TFEA. Typical Procedure. To **1a** (100 mg, 0.51 mmol) in TFEA (5 mL) was added HTIB (399 mg, 1.02 mmol) portionwise over 10 min under ice cooling in an argon atmosphere. After the reaction mixture was stirred for 5 min, 10% Na_2CO_3 (20 mL) was added under cooling. The aqueous layer was extracted with AcOEt (30 mL × 2), and the combined organic layer was washed with brine (30 mL), dried over Na_2-

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SO_4, and concentrated. The residue was chromatographed on a column of silica gel with AcOEt as an eluent to give **2a** (80 mg, 82%).

1-Methoxy-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (2a): mp 129−131 °C (AcOEt) (lit.[10] mp 130−132 °C).

6-Fluoro-1-methoxy-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (2d): white crystals; mp 110−112 °C (AcOEt/hexane); IR (KBr) 1730, 1680, 1655, 1365, 1165 cm^{-1};^{1}H NMR ($CDCl_3$) δ 2.12−2.70 (m, 4H), 3.78 (s, 3H), 6.04 (dd, J_{H-F} = 13.5 Hz, J_{H-H} = 1.6 Hz, 1H), 6.32 (dt, J_{H-H} = 10.0 Hz, $J_{H-F\ =\ H-H}$ = 1.3 Hz, 1H), 6.70 (t, $J_{H-F=H-H}$ = 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.7, 25.8 (d, J_{C-F} = 1.7 Hz), 61.8 (d, J_{C-F} = 22.3 Hz), 64.8, 111.0 (d, J_{C-F} = 9.5 Hz), 130.1 (d, J_{C-F} = 1.6 Hz), 143.7 (d, J_{C-F} = 5.0 Hz), 171.6, 172.7 (d, J_{C-F} = 287.9 Hz), 185.7 (d, J_{C-F} = 15.6 Hz); EI-MS *m*/*z* 211 (M^+, 8.5), 181 (39.3), 153 (100), 126 (32.5), 124 (30.1), 109 (28.6), 96 (27.5). Anal. Calcd for $C_{10}H_{10}NO_3F$: C, 56.87; H, 4.77; N, 6.63. Found: C, 56.76; H, 4.71; N, 6.63.

7-Fluoro-1-methoxy-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (2e): white crystals; mp 116−118 °C (Et_2O/petroleum ether); IR (KBr) 1730, 1690, 1185 cm^{-1};^{1}H NMR ($CDCl_3$) δ 2.26 (t, *J* = 8.0 Hz, 2H), 2.57 (t, *J* = 8.0 Hz, 2H), 3.80 (s, 3H), 6.34−6.46 (m, 2H), 6.86 (dd, J_{H-H} = 10.0, 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.8, 27.6, 63.7 (d, J_{C-F} = 1.6 Hz), 65.4, 112.9 (d, J_{C-F} = 13.4 Hz), 129.7 (d, J_{C-F} = 3.9 Hz), 147.9 (d, J_{C-F} = 2.8 Hz), 154.3 (d, J_{C-F} = 269.4 Hz), 171.4, 177.2 (d, J_{C-F} = 22.3 Hz); EI-MS *m*/*z* 211 (M^+, 50.5), 180 (100), 151 (78.3), 137 (65.6), 124 (99.0), 109 (86.3), 96 (69.0). Anal. Calcd for $C_{10}H_{10}NO_3F$: C, 56.87; H, 4.77; N, 6.63. Found: C, 56.76; H, 4.78; N, 6.58.

1-Methoxy-7-methyl-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (2f): white crystals; mp 113−115 °C (AcOEt/hexane); IR (KBr) 1730, 1675, 1640, 1170 cm^{-1};^{1}H NMR ($CDCl_3$) δ 1.95 (d, *J* = 1.4 Hz, 3H), 2.15 (t, *J* = 7.8 Hz, 2H), 2.54 (t, *J* = 7.8 Hz, 2H), 3.78 (s, 3H), 6.36 (d, *J* = 9.7 Hz, 1H), 6.58−6.63 (m, 1H), 6.80 (dd, *J* = 9.7, 3.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.0, 26.1, 27.7, 62.3, 65.2, 130.8, 137.8, 142.2, 146.9, 171.6, 185.0; EI-MS *m*/*z* 207 (M^+, 31.4), 176 (100), 147 (36.3), 133 (60.2), 120 (42.8), 91 (32.2). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.51; H, 6.23; N, 6.76.

6-Chloro-1-methoxy-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (2g): white crystals; mp 179−180 °C (AcOEt); IR (KBr) 1730, 1665, 1345 cm^{-1};^{1}H NMR ($CDCl_3$) δ 2.03−2.31 (m, 1H), 2.32−2.80 (m, 3H), 3.84 (s, 3H), 6.39 (dd, *J* = 9.8, 1.8 Hz, 1H), 6.66 (d, *J* = 1.8 Hz, 1H), 6.90 (d, *J* = 9.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.0, 27.1, 64.6, 64.9, 129.4, 130.5, 147.5, 154.6, 171.4, 182.8; EI-MS *m*/*z* 229 (M^+ + 2, 2.6), 227 (M^+, 6.9), 197 (53.2), 162 (100), 142 (47.5), 134 (54.1). Anal. Calcd for $C_{10}H_{10}NO_3Cl$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.60; H, 4.42; N, 6.00.

7-Chloro-1-methoxy-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (2h): white crystals; mp 135−138 °C (AcOEt/hexane); IR (KBr) 1720, 1680, 1315 cm^{-1};^{1}H NMR ($CDCl_3$) δ 2.24 (t, *J* = 7.9 Hz, 2H), 2.57 (t, *J* = 7.9 Hz, 2H), 3.80 (s, 3H), 6.47 (d, *J* = 10.0 Hz, 1H), 6.87 (dd, *J* = 10.0, 2.8 Hz, 1H), 7.01 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.9, 27.4, 63.8, 65.4, 129.9, 134.7, 142.9, 147.4, 171.4, 177.3; EI-MS *m*/*z* 229 (M^+ + 2, 14.9), 227 (M^+, 43.9), 196 (94.1), 167 (65.8), 162 (70.5), 140 (83.4), 132 (100). Anal. Calcd for $C_{10}H_{10}NO_3Cl$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.59; H, 4.30; N, 6.13.

1-Oxo-2-methoxyl-3,4-dihydro-2*H*-isoquinoline-3-spiro-1′-(cyclohexa-2′,5′-dien-4′-one) (2i): white crystals; mp 133−135 °C (AcOEt/hexane); IR (KBr) 1670, 1635, 1325, 1020 cm^{-1};^{1}H NMR ($CDCl_3$) δ 3.32 (s, 2H), 3.90 (s, 3H), 6.35 (d, *J* = 10.2 Hz, 2H), 6.96 (d, *J* = 10.2 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.53 (td, *J* = 7.5, 1.4 Hz, 1H), 8.19 (dd, *J* = 7.5, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 39.9, 63.7, 64.9, 127.2, 127.4, 127.8, 128.5, 130.6, 133.2, 133.9, 146.7, 164.5, 184.1; EI-MS *m*/*z* 255 (M^+, 4.3), 225 (30.4), 118 (100), 90 (26.7). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.48; H, 4.91; N, 5.28.

6,7-Difluoro-1-methoxy-1*H*-quinolin-2-one (3): white crystals; mp 137−139 °C (AcOEt/hexane); IR (KBr) 1665, 1610, 1410, 1260 cm^{-1};^{1}H NMR ($CDCl_3$) δ 4.11 (s, 3H), 6.75 (d, J_{H-H} = 9.6 Hz, 1H), 7.36−7.50 (m, 2H), 7.58 (d, J_{H-H} = 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 63.1, 101.2 (d, J_{C-F} = 23.5 Hz), 115.8 (dd, J_{C-F} = 18.4, 1.7 Hz), 116.0 (dd, J_{C-F} = 5.9, 3.0 Hz), 123.2 (d, J_{C-F} = 3.3 Hz), 135.3 (dd, J_{C-F} = 10.6, 1.1 Hz), 137.0 (t, J_{C-F} = 2.1 Hz), 146.6 (dd, J_{C-F} = 246.5, 14.0 Hz), 152.3 (dd, J_{C-F} = 254.3, 14.5 Hz), 157.3; EI-MS *m*/*z* 211 (M^+, 71.2), 181 (100), 166 (30.1), 153 (59.1), 152 (56.1), 125 (29.5). Anal. Calcd for $C_{10}H_7NO_2F_2$: C, 56.88; H, 3.34; N, 6.63. Found: C, 56.81; H, 3.40; N, 6.59.

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