Synthesis of Spiro-Fused (C5)-Isoxazolino-(C4)-pyrazolones (1-Oxa-2,7,8-triazaspiro[4,4]-2,8-dien-6-ones) via 1,3-Dipolar Cycloaddition and Cycloelimination

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An efficient and selective method for the synthesis of spiro-fused (C5)-isoxazolino-(C4)-pyrazolones (**C**) is reported. The process consists of utilizing the Baylis−Hillman reaction—or a quicker, stepwise MAC procedure—to give **I** followed by 1,3-dipolar cycloaddition and Swern oxidation to give *β*-ketoesters **H**, which were condensed with hydrazine derivatives to provide hydrazones that underwent cycloelimination. These novel spiro-fused (C5)-isoxazolino-(C4)-pyrazolones were confirmed by spectroscopic analysis as well as single-crystal X-ray of **5**. We also concluded that all condensations/cycloeliminations, except with hydrazine itself, were more effective with catalysts or higher reaction temperatures. For example, $TiCl_4$ was an efficient catalyst for hydrazone formation and cycloelimination with methylhydrazine, while phenyl-, benzyl-, and (4-methoxyphenyl)hydrazine reacted effectively without catalyst in refluxing xylene.

Introduction

Our interest in isoxazolines[1,2] and pyrazolones[3] along with previous work in spirocyclic heterocycles (**A** and **B**, Figure 1)[4] has led us to the design and synthesis of novel isoxazoline- and pyrazolone-containing spirocyclic heterocycles **C**. Indeed, isoxazoline- and cyclohexadiene-containing molecules have been isolated as secondary metabolites (cf. **D**) and some have shown biological activity.[5] The synthesis of spiro (C5)-isoxazolino-(C4)-pyrazolones derivatives has been reported by pyrazolone formation, Knoevenagel condensation, and then isoxazoline formation.[6] In that work, the 1,3-dipolar cycloaddition, shown in Figure 2, led to a mixture of regioisomers **E** and **F** as well as both diastereomers of each regioisomer due to mixture of *E*- and *Z*-isomers of the starting alkene.[7] Structural similarities between spiro compounds **G** and **C** also make the synthesis of **G** worth mentioning.[8] In this case, the alkene underwent regioselective 1,3-dipolar cycloaddition with nitrones to provide the spiro-fused isoxazolidine. Recently, compounds containing

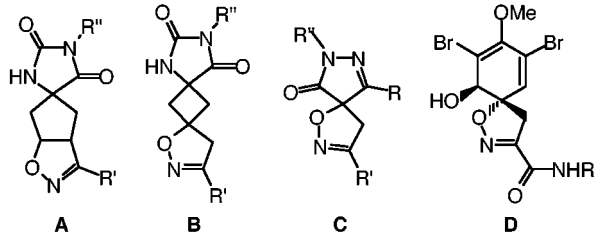

Figure 1. Spiro-fused heterocyclic systems.

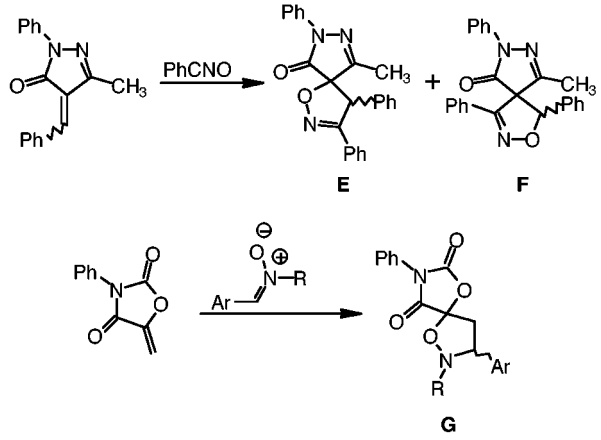

Figure 2. Mixed bis-heterocyclic spiro compounds.

isoxazol(in)es and molecules containing pyrazol(on)es have been shown to activate chloride channeling in the cystic fibrosis transmembrane conductance regulator (CFTR), and the compounds reported here (**C**), containing both types of heterocycles, could also be potential activators.[9]

(1) Kantorowski, E. J.; Kurth, M. J. *J. Org. Chem.* **1997**, *62*, 6797−6803.

(2) Lorsbach, B. A.; Bagdanoff, J. T.; Miller, R. B.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 2244−2250.

(3) Kizer, D. E.; Miller, R. B.; Kurth, M. J. *Tetrahedron Lett.* **1999**, *40*, 3535−3538.

(4) (a) Park, K. H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 113−117. (b) Park, K. H.; Kurth, M. J. *J. Org. Chem.* **2000**, *65*, 3520−3524. (c) Park, K. H.; Ehrler, J.; Spoerri, H.; Kurth, M. J. *J. Comb. Chem.* **2001**, *3*, 171−176.

(5) (a) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Magno, S.; Pansini, M. *J. Nat. Prod.* **1999**, *62*, 590−593. (b) Ciminiello, P.; Fattorusso, E.; Magno, S.; Pansini, M. *J. Nat. Prod.* **1994**, *57*, 1564−1569. (c) Rodríguez, A. D.; Piña, I. C. *J. Nat. Prod.* **1993**, *56*, 907−914.

(6) Lo Vecchio, G.; Gattuso, M.; Stagno D'Alcontres, G. *Gazz. Chim. Ital.* **1969**, *99*, 121−132.

(7) While cycloaddition of **1** → **3** is completely regioselective, we have not investigated regioselectivity in trisubstituted alkene versions of **1**.

(8) Benavides, A.; Martínez, R.; Jiménez-Vázquez, H. A.; Delgado, F.; Tamariz, J. *Heterocycles* **2001**, *55*, 469−485.

(9) Galietta, L. J. V.; Springsteel, M. F.; Eda, M.; Niedzinski, E. J.; By, K.; Haddadin, M. J.; Kurth, M. J.; Nantz, M. H.; Verkman, A. S. *J. Biol. Chem.* **2001**, *276*, 19723−19728.

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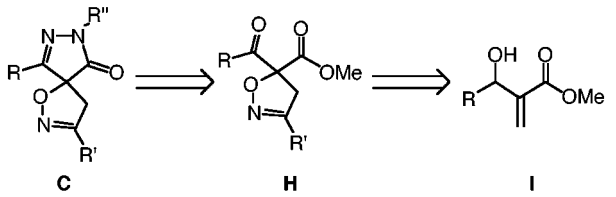


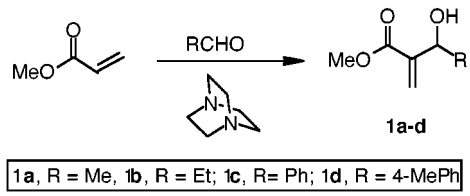
Figure 3. Retrosynthetic approach to isoxazolinopyrazolones.

The Baylis−Hillman reaction—a valuable carbon−carbon bond-forming reaction in organic chemistry—provides, in one pot, the α-anion equivalent of an electron deficient alkene.[10] The electrophile is usually an aldehyde, and the most common catalyst is DABCO (1,4-diazabicyclo[2.2.2]octane). In addition, Baylis−Hillman adducts have been widely utilized as intermediates in the synthesis of various target molecules.[11] If these same intermediates are visualized in our approach to **C**, methyl acrylate could provide allylic alcohol adduct **I** (Figure 3). 1,3-Dipolar cycloaddition of nitrile oxides with this Baylis−Hillman adduct followed by oxidation should give ketone **H** regioselectively. We reasoned that treating this *β*-ketoester with monosubstituted hydrazines would deliver the corresponding hydrazone which, by cycloelimination of methanol via an intramolecular hydrazone condensation with the ester, would provide the target isoxazolinopyrazolones (**C**).

Results and Discussion

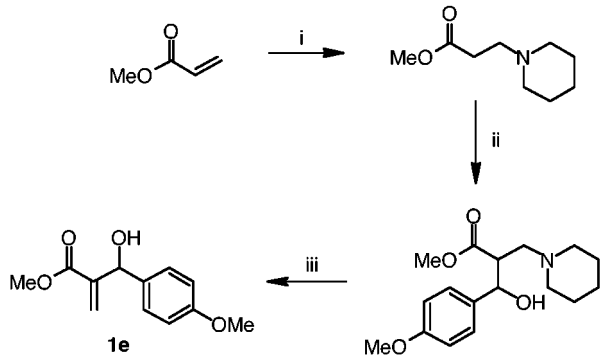
Our synthesis commenced with the Baylis−Hillman reaction between methyl acrylate and various aliphatic and aromatic aldehydes. Typical reports of the DABCO-catalyzed Baylis−Hillman reaction require reaction times of several days to weeks, but the reaction is quite dependent on both the activated alkene and the aldehyde electrophile. As a result, many investigations into new catalysts and alternative reaction conditions have been attempted to expedite reaction times and increase yields.[12] One account of the reaction between *tert*-butyl acrylate and benzaldehyde under normal Baylis−Hillman conditions provided the product in 90% yield, but the reaction took 4 weeks.[10b] Even more drastic cases are documented in the literature (33 and 62 days;[13] 33, 38, 40, and 63 days;[14] 48 days[15]). Despite these drawbacks and limitations of the Baylis−Hillman reaction, we were able to synthesize several allylic alcohols **1a**−**d** in acceptable yields using standard procedures (Scheme 1).

Scheme 1. Baylis−Hillman Reaction



1a, R = Me, **1b**, R = Et; **1c**, R= Ph; **1d**, R = 4-MePh

Scheme 2. Alternative MAC Route to Baylis−Hillman Adducts of *p*-Anisaldehyde[a]



[a] Key: (i) piperidine, THF, rt; (ii) (a) LDA, THF, −78 °C, (b) $ZnCl_2$, THF, (c) *p*-anisaldehyde; (iii) MCPBA, DCM, rt.

Baylis−Hillman problems previously reported with *p*-anisaldehyde were confirmed in our hands. We found that a seldom-used,[16] stepwise, "MAC" procedure (Scheme 2) consisting of (i) *M*ichael addition of an unhindered secondary amine (piperidine), (iia) lithium enolate formation of the *β*-aminoester with LDA, (iib) conversion to its zincate with $ZnCl_2$,[17] (iic) *a*ldol reaction with various aldehydes, and (iii) *N*-oxide formation from the *γ*-amino alcohol with MCPBA followed by concomitant *C*ope elimination[18,19] allowed us to obtain Baylis−Hillman adduct **1e** 1 day after the process was initiated. While this work was in progress, an alternative protocol for the "stepwise" Baylis−Hillman reaction, which employs lithium phenyl selenide, was published.[20]

With the allylic alcohols (**1a**−**e**) in hand, we next investigated their 1,3-dipolar cycloaddition with various

(10) (a) Basavaiah, D.; Rao, P. D.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001−8062. (b) Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 51, pp 201−350.

(11) (a) Hoffmann, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849−3859. (b) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, *58*, 2151−2161. (c) Maguire, R. J.; Mulzer, J.; Bats, J. W. *J. Org. Chem.* **1996**, *61*, 6936−6940. (d) Basavaiah, D.; Muthukumaran, K. *Tetrahedron* **1998**, *54*, 4943−4948. (e) Kim, J. N.; Lee, K. Y.; Kim, H. S.; Kim, T. Y. *Org. Lett.* **2000**, *2*, 343−345. (f) Basvaiah, D.; Krishnamacharyulu, M.; Suguna Hyma, R.; Sarma, P. K. S.; Kumaragurubaran, N. *J. Org. Chem.* **1999**, *64*, 1197−1200. (g) Ravichandran, S. *Synth. Commun.* **2001**, *31*, 2055−2057. (h) Ravichandran, S. *Synth. Commun.* **2001**, *31*, 2185−2188. (i) Masunari, A.; Ishida, E.; Trazzi, G.; Almeida, W. P.; Coelho, F. *Synth. Commun.* **2001**, *31*, 2127−2136. (j) Alcaide, B.; Almendros, P.; Aragoncillo, C. *J. Org. Chem.* **2001**, *66*, 1612−1620. (k) Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **1998**, *39*, 8609−8612. (l) Lawrence, N. J.; Crump, J. P.; McGown, A. T.; Hadfield, J. A. *Tetrahedron Lett.* **2001**, *42*, 3939−3941. (m) Basavaiah, D.; Kumaragurubaran, N. *Tetrahedron Lett.* **2001**, *42*, 477−479. (n) Mateus, C. R.; Feltrin, M. P.; Costa, A. M.; Coelho, F.; Almeida, W. P. *Tetrahedron* **2001**, *57*, 6901−6908.

(12) (a) Rafel, S.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 1521−1522. (b) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183−7189. (c) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539−1542. (d) Aggarwal, V. K.; Mereu, A. *J. Chem. Soc., Chem. Commun.* **1999**, 2311−2312. (e) Kundu, M. K.; Mukherjee, S. B.; Balu, N.; Padmakumar, R.; Bhat, S. V. *Synlett* **1994**, 444. (f) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413−5418. (g) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219−10220.

(13) Fort, Y.; Berthe, M. C.; Caubere, P. *Tetrahedron* **1992**, *48*, 6371−6384.

(14) Poly, W.; Schomburg, D.; Hoffmann, H. M. R. *J. Org. Chem.* **1988**, *53*, 3701−3710.

(15) Gilbert, A.; Heritage, T. W.; Isaacs, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 969−972.

(16) Brand, M.; Drewes, S. E.; Roos, G. H. P. *Synth. Commun.* **1986**, *16*, 883−889.

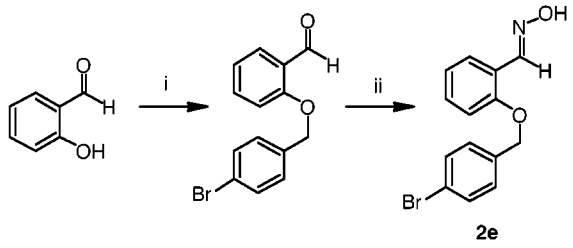
(17) Kurth, M. J.; Ahlberg Randall, L. A.; Chen, C.; Melander, C.; Miller, R. B.; McAlister, K.; Reitz, G.; Kang. R.; Nakatsu, T.; Green, C. *J. Org. Chem.* **1994**, *59*, 5862−5864.

(18) We have found in previous studies that cope eliminations of *β*-amino ester *N*-oxides, unsubstituted at the α-position, are quite facile. See: Sammelson, R. E.; Kurth, M. J. *Tetrahedron Lett.* **2001**, *42*, 3419−3422.

(19) We have also examined Hofmann eliminations of these systems and found that quaternization with methyl iodide led to ∼50% retro-Aldol product upon elimination with diisopropylethylamine. Quaternization with allyl iodide, however, did not give any retro-Aldol product upon elimination. Similarly, MCPBA-mediated Cope eliminations also showed no retro-Aldol, and thus, we have not further investigated the ambiguity of the Hofmann conditions at this time.

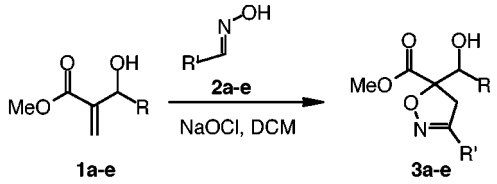
(20) Jauch, J. *J. Org. Chem.* **2001**, *66*, 609−611.

Scheme 3. Synthesis of Aldoxime 2e from Salicylaldehyde[a]

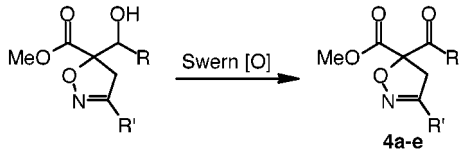


[a] Key: (i) 4-BrBnBr, Na_2CO_3, TBAI, DMF, 100 °C; (ii) $H_2NON{\cdot}HCl$, NaOAc, THF/EtOH/H_2O.

Scheme 4. 1,3-Dipolar Cycloaddition of Nitrile Oxides with Baylis−Hillman Adducts



Scheme 5. Swern Oxidation of Cycloadducts To Provide *β*-Keto Esters



nitrile oxides. The requisite aldoximes (see Scheme 4) **2a**−**d** were synthesized from the corresponding aldehydes by reaction with hydroxylamine, while aldoxime **2e** was prepared in two steps (Scheme 3) by *O*-alkylation of salicylaldehyde with 4-bromobenzyl bromide, sodium carbonate, and catalytic TBAI in DMF at 100 °C. This aldehyde was then converted into aldoxime **2e** by reaction with hydroxylamine.

Employing bleach as oxidant converts oximes into nitrile oxides in situ,[21] and we selected this convenient, efficient method to generate nitrile oxides from aldoximes **2a**−**e**. The nitrile oxides were reacted with Baylis−Hillman adducts **1a**−**e** (**1a** with the nitrile oxide of **2a**, **1b** with **2b**, etc.) to give the corresponding isoxazolines **3a**−**e** (Scheme 4). Diastereoselectivity for these cycloadditions ranged from 1.4 to 2.6. In all cases, hydrogen bonding of the allylic alcohol with the nitrile oxide gives preference for the syn diastereomer; X-ray crystallographic analysis of the major diastereomer of **3e** confirms this diastereoselectivity. We generally did not separate the diastereomers or even purify these intermediates since the subsequent Swern oxidation (Scheme 5) removes the second stereocenter and proceeds efficiently on crude isoxazoline substrates. The structures and overall yields of these *β*-ketoesters are displayed in Table 1.

Condensation of *β*-ketoesters **4a**−**e** with hydrazines was presumed to give the corresponding hydrazone that would then undergo cycloelimination to give the target isoxazolinopyrazolones (Scheme 6, Table 2). We found, in all cases, that the final cycloelimination commenced

(21) Sammelson, R. E.; Miller, R. B.; Kurth, M. J. *J. Org. Chem.* **2000**, *65*, 2225−2228.

Table 1. Structures of Isoxazolines 3 and 4 and Overall Yields of 4

3a−**e** and **4a**−**e**	R′	R′	isolated yield of **4** from **1** (%)
a	Me	2-ClPh	64
b	Et	4-MeOPh	76
c	Ph	2-Pyridyl	72
d	4-MePh	2-MeOPh	73
e	4-MeOPh	2-(4-BrBnO)Ph	66

Scheme 6. Hydrazone Formation and Cycloelimination To Afford Pyrazolones

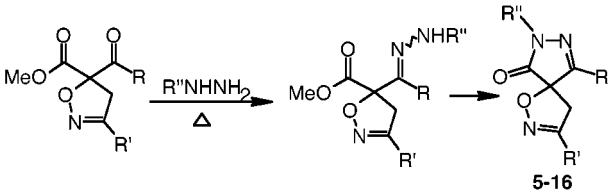


Table 2. Structures of Spiro-Isoxazolinopyrazolones 5−16 and Yields from 4a−e

	R	R′	R″	isolated yield (%)
5	Me	2-ClPh	Me	67
6	Me	2-ClPh	Ph	64
7	Et	4-MeOPh	Me	87
8	Et	4-MeOPh	Ph	72
9	Et	4-MeOPh	H	80
10	Et	4-MeOPh	Bn	77
11	Et	4-MeOPh	4-MeOPh	97
12	Ph	2-Pyridyl	Me	97
13	Ph	2-Pyridyl	Ph	44 (71)[a]
14	4-MePh	2-MeOPh	Me	72
15	4-MePh	2-MeOPh	Ph	58
16	4-MeOPh	2-(4-BrBnO)Ph	Me	45 (72)[b]

[a] Yield based on isolated hydrazone. [b] Yield based on isolated *β*-keto ester.

before all starting *β*-ketoester was consumed.[22] Indeed, hydrazone formation is difficult in most cases because of the steric hindrance of these ketones. The electron rich *p*-methoxyphenyl ketone further retarded the progress of this reaction, and 27% of starting *β*-ketoester was isolated upon workup and product purification. Fortunately, we found that TFA,[23] or even better, $TiCl_4$,[24] effectively catalyzed this conversion. Isomerization between the *E*- and *Z*-hydrazones must also be taken into account as only the *Z*-configuration is capable of cycloelimination.[25] Unfortunately, the *Z*-isomer is sterically less favored as evidenced by X-ray crystallographic analysis of the *E*-phenylhydrazone of **4c**; the corresponding *Z*-isomer was not detected. Thus, with the exception of hydrazine itself, these condensations/cycloeliminations were difficult without catalysts or high temperature. $TiCl_4$ was found to be an efficient catalyst for not only hydrazone formation but also cycloelimination of methylhydrazine with *β*-ketoesters, and phenyl-, benzyl-, and (4-methoxyphenyl)hydrazine were determined to react more efficiently in refluxing xylene. Finally, spectroscopic

(22) Pyrazolones were noticed as side products when α,α-disubstituted-*β*-keto esters and semicarbazide were reacted: Keay, B. A.; Rodrigo, R. *J. Am. Chem. Soc.* **1982**, *104*, 4725−4727.

(23) Tietze, L. F.; Evers, H.; Hippe, T.; Steinmetz, A.; Töpken, E. *Eur. J. Org. Chem.* **2001**, 1631−1634.

(24) Tita, T. T.; Kornet, M. J. *J. Heterocyclic Chem.* **1988**, *25*, 265−269.

(25) (a) Nakazawa, T.; Mizuta, Y.; Kawahara, A.; Miyamoto, E.; Muto, N. *Chem. Lett.* **1992**, 1125−1128. (b) Matsuda, E.; Aoto, M.; Takahashi, S.; Ono, H.; Tokumaru, K. *Chem. Lett.* **1992**, 1129−1132. (c) Zimmer, O.; Meier, H. *Chem. Ber.* **1981**, *114*, 2938−2946.

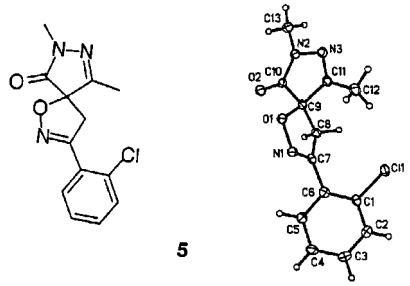


Figure 4. Computer-generated single-crystal X-ray structure of **5**.

and single-crystal X-ray analysis (cf. computer-generated X-ray structure of **5**, Figure 4) verified the formation of these novel spiro-fused (C5)-isoxazolino-(C4)-pyrazolones.

Conclusion

Spiro-fused (C5)-isoxazolino-(C4)-pyrazolones are prepared by a four-step procedure from methyl acrylate consisting of a Baylis−Hillman reaction (or stepwise MAC procedure—*M*ichael addition, *a*ldol reaction, and *C*ope elimination), 1,3-dipolar cycloaddition with nitrile oxides, Swern oxidation, and hydrazone formation with concomitant cycloelimination. The novel spiro-fused isoxazolinopyrazolone (3,7,9-substituted-1-oxa-2,7,8-triazaspiro[4.4]nona-2,8-dien-6-one) are constrcuted from three diversity inputs—RCHO, R′CH═NOH, and R″NHNH$_2$ (see **C**, Figure 1)—by a procedure which appears suitable for combinatorial library production.

Experimental Section

General Procedures. All reactions, unless otherwise noted, were performed under an inert atmosphere of dry nitrogen. LDA (2.0 M solution in heptane/THF/ethylbenzene), MCPBA (80−85%), hydrazines, and $TiCl_4$ (1.0 M in DCM) were purchased from Aldrich and used as received. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately prior to use. Methylene chloride was distilled from CaH_2, and toluene, from K. Triethylamine was distilled from CaH_2 and stored over KOH. DMF was dried and distilled from CaH_2 onto 3 Å molecular sieves. A 1.3 M solution of $ZnCl_2$ in THF was prepared by first fusing commercially available $ZnCl_2$ with a Bunsen burner flame under high vacuum. The resulting anhydrous $ZnCl_2$ was allowed to cool under N_2 and then dissolved in the appropriate volume of dry THF. Melting points are uncorrected. All infrared spectra were analyzed neat by reflective FT-IR. ^{1}H- and ^{13}C NMR were measured in $CDCl_3$ at 300 and 75 MHz, respectively; unless otherwise noted. $CDCl_3$ or DMSO-d_6 was used as internal standard for ^{13}C NMR while tetramethylsilane was added as internal standard for ^{1}H NMR. Elemental analyses were determined at MidWest Microlab, Indianapolis, IN. Known aldoximes **2a**−**d** were prepared from their corresponding aldehydes using standard methods.

General Procedure for the Baylis−Hillman Reaction Providing Adducts 1a−d. Aliphatic (1.5 equiv) or aromatic aldehyde (0.67 equiv) was mixed with methyl acrylate (1.0 equiv) and DABCO (0.1 equiv). This solution was allowed to stand at room temperature for 7−10 d. The reaction was diluted with ether and extracted twice with water. The organic layer was dried with Na_2SO_4, filtered, and concentrated to afford the product.

Methyl 2-(1-hydroxyethyl)acrylate (1a):[11b] IR 3419, 2976, 2953, 1710, 1262, 1092 cm^{-1}; ^{1}H NMR δ 1.37 (d, J = 6.6 Hz, 3H), 3.2 (br, 1H), 3.78 (s, 3H), 4.68 (m, 1H), 5.87 (t, J = 1.1 Hz, 1H), 6.22 (t, J = 0.9 Hz, 1H); ^{13}C NMR δ 22.1, 51.7, 66.5, 123.9, 143.5, 166.9.

Methyl 2-(1-hydroxypropyl)acrylate (1b):[12a] IR 3438, 2966, 1711, 1274, 1158, 1099, 954 cm^{-1}; ^{1}H NMR δ 0.95 (t, J = 7.3 Hz, 3H), 1.68 (m, 2H), 2.6 (br, 1H), 3.79 (s, 3H), 4.33 (t, J = 6.4 Hz, 1H), 5.80 (d, J = 1.3 Hz, 1H), 6.24 (d, J = 1.3 Hz, 1H); ^{13}C NMR δ 10.0, 29.0, 51.8, 72.9, 125.1, 142.0, 167.0.

Methyl 2-(hydroxyphenylmethyl)acrylate (1c):[11c] IR 3448, 3062, 2952, 1713, 1439, 1278, 1148 cm^{-1}; ^{1}H NMR δ 3.1 (br, 1H), 3.73 (s, 3H), 5.57 (s, 1H), 5.84 (d, J = 6.9 Hz, 1H), 6.35 (d, J = 6.9 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR δ 51.6, 72.5, 125.5, 126.5, 127.5, 128.1, 141.2, 141.9, 166.4.

Methyl 2-(hydroxy(4-methylphenyl)methyl)acrylate (1d):[11d] mp 41−42 °C; IR 3432, 3013, 2951, 1708, 1437, 1270, 1146, 1036, 814 cm^{-1}; ^{1}H NMR δ 2.33 (s, 3H), 2.9 (br, 1H), 3.71 (s, 3H), 5.53 (s, 1H), 5.85 (s, 1H), 6.33 (s, 1H), 7.15 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H); ^{13}C NMR δ 21.1, 51.8, 72.9, 125.7, 126.5, 129.0, 137.4, 138.3, 141.9, 166.7.

Methyl 2-(hydroxy(4-methoxyphenyl)methyl)acrylate (1e).[12d] Methyl acrylate (596 mg, 6.92 mmol) in 10 mL of THF was cooled to 0 °C, and piperidine (583 mg, 6.85 mmol) was added dropwise over 10 min. The reaction was allowed to warm to room temperature and stand for 5 h and then was concentrated in vacuo to give methyl 3-(piperidin-1-yl)propionate:[26] IR 2933, 2852, 2775, 1738, 1437, 1169, 1000 cm^{-1}; ^{1}H NMR δ 1.43 (m, 2H), 1.57 (m, 4H), 2.39 (br t, J = 4.8 Hz, 4H), 2.52 (t, J = 7.5 Hz, 2H), 2.66 (t, J = 7.5 Hz, 2H), 3.68 (s, 3H); ^{13}C NMR δ 24.2, 25.9, 32.0, 51.6, 54.2, 173.1. This β-aminoester was dissolved in THF, cooled to −78 °C, and treated with LDA (3.43 mL, 6.85 mmol) for 30 min. The reaction was brought to 0 °C, $ZnCl_2$ (5.7 mL, 7.45 mmol) was added, and after 15 min the temperature was returned to −78 °C and *p*-anisaldehyde (970 mg, 7.1 mmol) added. After 30 min the reaction was quenched with 1.0 M aqueous NH_4Cl, the layers were separated, and the aqueous layer was extracted twice with DCM. The combined organic layers were dried and concentrated to provide the crude aldol product as a ∼2:1 mixture of diastereomers, which were purifed but not separated. Cope elimination followed MCPBA (1.6 g, 7.45 mmol) oxidation in DCM at room temperature over 4 h and gave **1e** (890 mg, 58%) after chromatography: IR 3459, 3001, 2950, 2836, 1719, 1511, 1248 cm^{-1}; ^{1}H NMR δ 3.0 (br, 1H), 3.72 (s, 3H), 3.80 (s, 3H), 5.53 (s, 1H), 5.86 (d, J = 0.9 Hz, 1H), 6.33 (d, J = 0.9 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 51.8, 55.1, 72.4, 113.6, 125.3, 127.8, 133.4, 142.1, 159.0, 166.6.

2-((4-Bromobenzyl)oxy)benzaldoxime (2e). 4-Bromobenzyl bromide (9.33 g, 37.3 mmol) and 2-hydroxybenzaldehyde (5.70 g, 46.7 mmol) were stirred in 40 mL of DMF. Sodium carbonate (9.96 g, 94 mmol) and a catalytic amount of TBAI were added, and the reaction was heated to 100 °C. The heating mantel was removed after 8 h and allowed to cool to room temperature before the addition of 200 mL ether and 200 mL of H_2O. The layers were separated, and the aqueous portion was extracted with 100 mL of ether. The combined organics were then washed with 100 mL of H_2O four times and once with brine. The organic layer was dried with Na_2SO_4, filtered, and rotoevaporated to give 2-((4-bromobenzyl)oxy)benzaldehyde[27] (6.83 g, 63%) after recrystallization in ethanol: IR 3032, 2946, 2870, 2766, 1681, 1597, 1480, 1240, 998, 748 cm^{-1}; ^{1}H NMR δ 5.15 (s, 2H), 7.03 (m, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.53 (m, 3H), 7.86 (d, J = 7.8 Hz, 1H), 10.54 (s, 1H); ^{13}C NMR δ 69.7, 112.9, 121.2, 122.2, 125.1, 128.7, 128.9, 131.9, 135.0, 135.9, 160.6, 189.5. This aldehyde (6.83 g, 23.4 mmol) was dissolved in THF−EtOH−H_2O (20, 10, 10 mL), and hydroxylamine hydrochloride (3.27 g, 47 mmol) was added followed by sodium acetate (5.77 g, 70 mmol). This solution was stirred at room temperature for 6 h. DCM (100 mL) and H_2O (50 mL) were added directly to the reaction flask. The layers were separated, and the aqueous layer was extracted two additional times with DCM. The combined organic layers were dried, filtered, and concentrated to give **2e** (6.58 g, 92%) as a white solid: mp 135−136.5 °C; IR 3246,

(26) Das, S.; Dileep Kumar, J. S.; Shivaramayya, K.; George, M. V. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1797−1799.
(27) Hellwinkel, D.; Göke, K. *Synthesis* **1995**, 1135−1141.

3014, 2915, 2869, 1601, 1493, 1453, 1244, 968, 742 cm^{-1}; ^1H NMR δ 5.07 (s, 2H), 6.91 (d, J = 8.3 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 7.30 (m, 3H), 7.51 (d, J = 7.9 Hz, 2H), 7.73 (d, J = 7.7 Hz, 1H), 8.54 (s, 1H), 8.74 (s, 1H); ^{13}C NMR δ 69.6, 112.5, 120.9, 121.3, 122.0, 126.9, 128.9, 131.2, 131.8, 135.5, 146.3, 156.4. Anal. Calcd for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; N, 4.58. Found: C, 55.09; H, 4.03; N, 4.28.

General Procedure for the 1,3-Dipolar Cycloaddition of Alkenes 1a−e with Nitrile Oxides Formed in Situ from Aldoximes 2a−e To Afford Isoxazolines 3a−e. Baylis−Hillman adduct (1.0 equiv) and aldoxime (1.0−1.5 equiv) were dissolved in DCM, and the solution was cooled to 0 °C. Bleach containing 5.25% NaOCl by weight (1.8−3.0 equiv) was added dropwise to the vigorously stirring solution over 30−45 min. The biphasic mixture was allowed to warm to room temperature and stirred for 8 h overnight. An additional volume of water (equal to the volume of bleach) was added, and the layers were separated. The aqueous layer was extracted two to three additional times with DCM, and the combined organic layers were dried with sodium sulfate, filtered, and rotoevaporated to give the crude product, which was carried onto the next step as a mixture of diastereomers.

General Procedure for the Swern oxidation of Secondary Alcohols 3a−e To Provide β-Keto Esters 4a−e. Oxalyl chloride (1.1 equiv) in DCM was cooled to −78 °C and DMSO (2.2 equiv) added dropwise and stirred for 5 min. This activated DMSO was transferred via cannula into a solution of alcohol **3** (1.0 equiv) in DCM at −78 °C. After 15 min, triethylamine (4.4 equiv) was added and then the dry ice/acetone bath removed. The reaction was allowed to proceed until it came to room temperature (∼60 min) at which time water was added. The layers were separated, and the organic layer was washed with water, 1 M sodium carbonate, and water (2×). The organic layer was then dried and concentrated to give a yellowish solid (except **4a**), which was recrystallized from methanol or ethanol to give the purified product.

Methyl 5-Acetyl-3-(2-chlorophenyl)-4,5-dihydroisoxazolo-5-carboxylate (4a). Following the general procedure for the 1,3-dipolar cycloaddition, alkene **1a** (1.00 g, 7.68 mmol), aldoxime **2a** (1.20 g, 7.68 mmol), and bleach (19.6 g, 13.8 mmol) gave **4a** (1.44 g, 64%) after Swern oxidation: IR 2952, 1729, 1434, 1354, 1283 cm^{-1}; ^1H NMR δ 2.44 (s, 3H), 3.86 (s, 3H), 3.98 (d, J = 18 Hz, 1H), 4.07 (d, J = 18 Hz, 1H), 7.37 (m, 3H), 7.61 (dd, J = 7.5 and 1.8 Hz, 1H); ^{13}C NMR δ 25.8, 43.1, 53.6, 93.0, 127.0, 127.3, 130.65, 130.67, 131.5, 132.9, 156.4, 167.7, 202.2.

Methyl 3-(4-Methoxyphenyl)-5-propanoyl-4,5-dihydroisoxazolo-5-carboxylate (4b). Following the general procedure for the 1,3-dipolar cycloaddition, alkene **1b** (4.12 g, 28.6 mmol), aldoxime **2b** (5.19 g, 34.3 mmol), and bleach (87.5 g, 61.7 mmol) gave **3b**. Major diastereomer: mp 104−105 °C; IR 3250, 3007, 2967, 2934, 1730, 1608, 1255 cm^{-1}; ^1H NMR δ 1.05 (t, J = 7.5 Hz, 3H), 1.43 (m, 2H), 2.5 (br, 1H), 3.56 (d, J = 17 Hz, 1H), 3.75 (d, J = 17 Hz, 1H), 3.81 (s, 3H), 3.83 (s, 3H), 4.01 (d, J = 9.6 Hz, 1H), 6.91 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 9.0 Hz, 2H); ^{13}C NMR δ 10.5, 24.5, 37.7, 53.0, 55.3, 73.7, 92.0, 114.1, 121.2, 128.4, 156.8, 161.3, 171.2. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.57; H, 6.39; N, 4.73. Following the general procedure for Swern oxidation, **3b** gave **4b** (6.34 g, 76%): mp 64−64 °C; IR 2939, 2840, 1746, 1727, 1608, 1517, 1256 cm^{-1}; ^1H NMR δ 1.11 (t, J = 7.1 Hz, 3H), 2.84 (q, J = 7.1 Hz, 2H), 3.830 (s, 3H), 3.834 (s, 3H), 3.87 (s, 2H), 6.92 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 7.2, 31.4, 41.4, 53.4, 55.2, 92.3, 114.1, 120.2, 128.4, 155.9, 161.4, 168.1, 205.5. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.92; H, 5.91; N, 4.81.

Methyl 5-Benzoyl-3-(2-pyridyl)-4,5-dihydroisoxazolo-5-carboxylate (4c). Following the general procedure for the 1,3-dipolar cycloaddition, alkene **1c** (2.00 g, 11.1 mmol), aldoxime **2c** (2.02 g, 16.6 mmol), and bleach (47.2 g, 33.3 mmol) gave **4c** (2.47 g, 72%) after Swern oxidation: mp 111−112 °C; IR 3081, 2966, 1783, 1733, 1656, 1246 cm^{-1}; ^1H NMR (400 MHz) δ 3.78 (s, 3H), 3.96 (d, J = 19 Hz, 1H), 4.65 (d, J = 19 Hz, 1H), 7.30 (ddd, J = 7.5, 4.9, and 1.2 Hz, 1H), 7.49 (td, J = 8.3 and 1.5 Hz, 2H), 7.61 (tt, J = 7.5 and 1.5 Hz, 1H), 7.74 (td, J = 7.6 and 1.8 Hz, 1H), 8.01 (dt, J = 7.9 and 1.0 Hz, 1H), 8.11 (dt, J = 8.3 and 1.2 Hz, 2H), 8.63 (ddd, J = 5.0, 1.7, and 1.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 42.2, 53.5, 92.1, 122.3, 125.1, 129.0, 130.2, 133.5, 134.3, 136.7, 148.2, 149.7, 158.3, 169.7, 189.9. Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.85; H, 4.58; N, 8.89.

Methyl 3-(2-Methoxyphenyl)-5-(4-methylbenzoyl)-4,5-dihydroisoxazolo-5-carboxylate (4d). Following the general procedure for the 1,3-dipolar cycloaddition, alkene **1d** (2.00 g, 9.70 mmol), aldoxime **2d** (1.76 g, 11.6 mmol), and bleach (27.6 g, 19.4 mmol) gave **4d** (2.50 g, 73%) after Swern oxidation: mp 115−116 °C; IR 3035, 2959, 2836, 1750, 1690, 1603, 1247 cm^{-1}; ^1H NMR δ 2.39 (s, 3H), 3.76 (s, 3H), 3.84 (s, 3H), 3.88 (d, J = 18 Hz, 1H), 4.61 (d, J = 18 Hz, 1H), 6.94 (m, 2H), 7.26 (d, J = 8.1 Hz, 2H), 7.37 (td, J = 7.9 and 1.8 Hz, 1H), 7.77 (dd, J = 7.9 and 1.8 Hz, 1H), 8.03 (d, J = 8.1 Hz, 2H); ^{13}C NMR δ 21.5, 44.6, 53.2, 55.3, 91.6, 111.3, 116.8, 120.6, 129.2, 129.3, 129.9, 130.7, 131.9, 144.9, 155.4, 157.4, 169.9, 189.8. Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.24; H, 5.52; N, 3.98.

Methyl 3-(2-((4-Bromobenzyl)oxy)phenyl)-5-(4-methoxybenzoyl)-4,5-dihydroisoxazolo-5 -carboxylate (4e). Following the general procedure for the 1,3-dipolar cycloaddition, alkene **1e** (272 mg, 1.22 mmol), aldoxime **2e** (374 mg, 1.22 mmol), and bleach (3.40 g, 2.4 mmol) gave **3e**. Major diastereomer: mp 150−151 °C; IR 3331, 2950, 1735, 1598, 1451, 1242, 1173, 998 cm^{-1}; ^1H NMR δ 2.76 (d, J = 3.5 Hz, 1H), 3.62 (d, J = 18 Hz, 1H), 3.73 (s, 3H), 3.76 (d, J = 18 Hz, 1H), 3.80 (s, 3H), 4.99 (d, J = 11 Hz, 1H), 5.03 (d, J = 11 Hz, 1H), 5.22 (d, J = 3.5 Hz, 1H), 6.79 (d, J = 8.8 Hz, 2H), 6.96 (m, 2H), 7.11 (d, J = 8.8 Hz, 2H), 7.31 (m, 3H), 7.55 (d, J = 7.9 Hz, 2H), 7.68 (dd, 7.7 and 1.5 Hz, 1H); ^{13}C NMR δ 39.8, 52.8, 55.3, 69.8, 73.8, 92.8, 112.5, 113.8, 118.2, 121.3, 122.1, 127.9, 128.9, 129.5, 129.7, 131.7, 131.8, 135.1, 156.4, 156.8, 159.6, 170.7. Anal. Calcd for $C_{26}H_{24}BrNO_6$: C, 59.33; H, 4.60; N, 2.66. Found: C, 59.40; H, 4.68; N, 2.54. Following the general procedure for Swern oxidation, **3e** gave **4e** (423 mg, 66%): IR 3075, 2952, 2839, 1754, 1739, 1680, 1597, 1491, 1451, 1259, 1165 cm^{-1}; ^1H NMR (400 MHz) δ 3.72 (s, 3H), 3.84 (d, J = 18 Hz, 1H), 3.89 (s, 3H), 4.53 (d, J = 18 Hz, 1H), 5.09 (s, 2H), 6.94 (m, 3H), 7.00 (td, J = 7.5 and 1.0 Hz, 1H), 7.30 (d, J = 8.6 Hz, 2H), 7.37 (ddd J = 8.5, 7.5, and 1.8 Hz, 1H), 7.51 (d, J = 8.6 Hz, 2H), 7.75 (dd, J = 7.8 and 1.8 Hz, 1H), 8.09 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz) δ 44.7, 53.3, 55.5, 69.9, 92.0, 112.7, 113.9, 117.7, 121.4, 122.1, 126.2, 129.1, 129.9, 131.8, 131.9, 132.5, 135.2, 155.6, 156.5, 164.1, 170.0, 188.7. Anal. Calcd for $C_{26}H_{22}BrNO_6 \cdot 0.25H_2O$: C, 59.05; H, 4.29; N, 2.65. Found: C, 58.96; H, 4.19; N, 2.57.

General Methods for the Conversion of β-Keto Esters 4a−e into Their Corresponding Hydrazones and Cycloelimination To Furnish Spiro-Fused Isoxazolinopyrazolones 5−16. Method A. Reaction of β-keto ester **4** with hydrazine ($R''NHNH_2$) was carried out in toluene or xylene at 110 or 138 °C, respectively.

Method B (TFA Mediated). Reaction of β-keto ester **4** with hydrazine ($R''NHNH_2$) was carried out with 2% TFA in acetonitrile or DCM at 65 °C or reflux, respectively.

Method C (TiCl4 Mediated). β-Keto ester **4**, TEA, and hydrazine ($R''NHNH_2$) were combined and cooled to 0 °C. $TiCl_4$ was added dropwise over 5 min, and then the reaction was allowed to come to room temperature. The dark mixture was then heated to 100 °C.

3-(2-Chlorophenyl)-7,9-dimethyl-1-oxa-2,7,8-triazaspiro-[4.4]nona-2,8-dien -6-one (5). Following general method B, **4a** (620 mg, 2.20 mmol) and methylhydrazine (176 μL, 3.3 mmol) gave **5** (409 mg, 67%): mp 107−108 °C; IR 3000, 2850, 1716, 1431, 1079, 1038 cm^{-1}; ^1H NMR δ 2.14 (s, 3H), 3.31 (s, 3H), 3.75 (d, J = 18 Hz, 1H), 3.82 (d, J = 18 Hz, 1H), 7.41 (m, 3H), 7.69 (dd, J = 7.5 and 1.7 Hz, 1H); ^{13}C NMR δ 12.6, 31.6, 43.9, 85.8, 127.1, 127.3, 130.6, 131.0, 131.6, 132.8, 155.4, 157.3, 171.0. Anal. Calcd for $C_{13}H_{12}ClN_3O_2$: C, 56.22; H, 4.36; N, 15.13. Found: C, 56.21; H, 4.43; N, 15.15.

3-(2-Chlorophenyl)-9-methyl-7-phenyl-1-oxa-2,7,8-triazaspiro[4.4]nona-2,8-dien-6-one (6). Following general method B, **4a** (624 mg, 2.22 mmol) and phenylhydrazine (229 μL, 2.33 mmol) gave **6** (483 mg, 64%): mp 103−104 °C; IR 3064, 2999, 2921, 1705, 1595, 1497, 1433, 1367, 1306 cm^{-1}; ^1H NMR δ 2.23 (s, 3H), 3.86 (s, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.38 (m, 5H), 7.68 (dd, *J* = 7.9 and 1.8 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR δ 12.7, 44.3, 87.0, 118.5, 125.4, 126.9, 127.2, 128.8, 130.6, 131.0, 131.7, 132.8, 137.4, 155.4, 157.9, 169.2. Anal. Calcd for $C_{18}H_{14}ClN_3O_2$: C, 63.63; H, 4.15; N, 12.37. Found: C, 63.52; H, 4.07; N, 12.23.

9-Ethyl-3-(4-methoxyphenyl)-7-methyl-1-oxa-2,7,8-triazaspiro[4.4]nona-2,8-dien-6-one (7). Following general method C, **4b** (231 mg, 790 μmol), methylhydrazine (170 μL, 3.2 mmol), and $TiCl_4$ (500 μmol) gave **7** (265 mg, 87%): mp 74−75 °C; IR 3052, 2976, 2941, 2839, 1716, 1606, 1253, 897, 819 cm^{-1}; ^1H NMR δ 1.23 (t, *J* = 7.3 Hz, 3H), 2.43 (m, 2H), 3.32 (s, 3H), 3.49 (d, *J* = 17 Hz, 1H), 3.70 (d, *J* = 17 Hz, 1H), 3.86 (s, 3H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 9.1, 20.1, 31.3, 42.1, 55.2, 84.9, 114.1, 120.0, 128.5, 154.9, 161.4, 171.4. Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.63. Found: C, 62.38; H, 5.89; N, 14.46.

9-Ethyl-3-(4-methoxyphenyl)-7-phenyl-1-oxa-2,7,8-triazaspiro[4.4]nona-2,8-dien-6-one (8). Following general method A, **4b** (150 mg, 515 μmol) and phenylhydrazine (101 μL, 1.03 mmol) in xylene gave **8** (130 mg, 72%): mp 119−120 °C; IR 3036, 2976, 1715, 1596, 1499, 1347, 1252, 819, 754 cm^{-1}; ^1H NMR δ 1.27 (t, *J* = 7.5 Hz, 3H), 2.48 (m, 2H), 3.57 (d, *J* = 17 Hz, 1H), 3.75 (d, *J* = 17 Hz, 1H), 3.79 (s, 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR δ 9.1, 20.3, 42.6, 55.2, 86.3, 114.2, 118.3, 119.9, 125.1, 128.6, 128.7, 137.5, 155.0, 161.5, 162.0, 169.8. Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.85; H, 5.48; N, 11.97.

9-Ethyl-3-(4-methoxyphenyl)-1-oxa-2,7,8-triazaspiro-[4.4]nona-2,8-dien-6-one (9). Following general method A, **4b** (525 mg, 1.8 mmol) and hydrazine hydrate (350 μL, 7.2 mmol) in toluene at room temperature gave **9** (390 mg, 80%): mp 170−171 °C; IR 3345, 3223, 3111, 2983, 1715, 1604, 1514, 1420, 1249, 1178, 869, 827 cm^{-1}; ^1H NMR δ 1.23 (t, *J* = 7.3 Hz, 3H), 2.43 (m, 2H), 3.52 (d, *J* = 17 Hz, 1H), 3.72 (d, *J* = 17 Hz, 1H), 3.85 (s, 3H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 8.6 (br, 1H); ^{13}C NMR δ 9.2, 19.9, 41.5, 84.3, 114.5, 120.2, 128.9, 155.9, 161.3, 161.5, 174.1.

7-Benzyl-9-ethyl-3-(4-methoxyphenyl)-1-oxa-2,7,8-triazaspiro[4.4]nona-2,8-dien-6-one (10). Following general method A, **4b** (150 mg, 515 μmol), TEA (208 mg, 2.06 mmol), and benzylhydrazine dihydrochloride (200 mg, 1.03 mmol) in xylene gave **10** (140 mg, 77%): mp 123−124 °C; IR 3032, 2976, 2930, 1714, 1606, 1412, 1349, 1253 cm^{-1}; ^1H NMR δ 1.08 (t, *J* = 7.3 Hz, 3H), 2.29 (m, 2H), 3.41 (d, *J* = 17 Hz, 1H), 3.60 (d, *J* = 17 Hz, 1H), 3.72 (s, 3H), 4.69 (d, *J* = 15 Hz, 1H), 4.76 (d, *J* = 15 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.24 (m, 5H), 7.49 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 9.3, 20.3, 42.3, 48.2, 55.3, 85.2, 114.2, 120.1, 127.7, 128.0, 128.5, 128.6, 135.8, 155.0, 161.5, 161.6, 171.4. Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.24; H, 5.77; N, 11.55.

9-Ethyl-3,7-bis(4-methoxyphenyl)-1-oxa-2,7,8-triazaspiro[4.4]nona-2,8-dien-6-one (11). Following general method A, **4b** (150 mg, 515 μmol), TEA (104 mg, 1.03 mmol), and (4-methoxyphenyl)hydrazine hydrochloride (180 mg, 1.03 mmol) in xylene gave **11** (190 mg, 97%): mp 122−123 °C; IR 2976, 2935, 2837, 1711, 1514, 1243 cm^{-1}; ^1H NMR δ 1.31 (t, *J* = 7.0 Hz, 3H), 2.52 (m, 2H), 3.58 (d, *J* = 17 Hz, 1H), 3.81 (d, *J* = 17 Hz, 1H), 3.83 (s, 3H), 3.86 (s, 3H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.80 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 9.4, 20.6, 42.8, 55.4, 55.5, 86.4, 114.1, 114.4, 120.3, 120.5, 128.7, 131.0, 155.0, 157.2, 161.7, 162.1, 169.5. Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.08. Found: C, 66.27; H, 5.58; N, 11.08.

7-Methyl-9-phenyl-3-(2-pyridyl)-1-oxa-2,7,8-triazaspiro-[4.4]nona-2,8-dien- 6-one (12). Following general method C, **4c** (202 mg, 650 μmol), methylhydrazine (140 μL, 2.6 mmol), and $TiCl_4$ (500 μmol) gave **12** (193 mg, 97%): mp 146−147 °C; IR 3067, 2929, 1715, 1582, 1469, 1359, 886, 774, 694 cm^{-1}; ^1H NMR δ 3.45 (s, 3H), 3.93 (s, 2H), 7.37 (m, 4H), 7.71 (dd, *J* = 7.5 and 1.8 Hz, 2H), 7.79 (td, *J* = 7.5 and 1.8 Hz, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 8.58 (dt, *J* = 4.8 and 0.9 Hz, 1H); ^{13}C NMR δ 31.8, 43.9, 85.3, 122.3, 124.8, 125.8, 128.5, 128.9, 130.7, 136.5, 147.6, 149.3, 155.2, 157.9, 171.7. Anal. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.96; H, 4.80; N, 18.16.

7,9-Diphenyl-3-(2-pyridyl)-1-oxa-2,7,8-triazaspiro[4.4]-nona-2,8-dien-6-one (13). Following general method C, **4c** (600 mg, 1.9 mmol), phenylhydrazine (230 μL, 2.3 mmol), and $TiCl_4$ (1.4 mmol) gave the corresponding hydrazone (205 mg, 27%) [mp 141−142 °C; IR 3206, 3059, 2949, 1757, 1600, 1584, 1494, 1249, 911, 698 cm^{-1}; ^1H NMR δ 3.82 (s, 3H), 4.03 (d, *J* = 18 Hz, 1H), 4.22 (d, *J* = 18 Hz, 1H), 6.83 (td, *J* = 7.6 and 0.9 Hz, 1H), 6.95 (d, 2H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.27 (ddd, *J* = 7.6, 4.8 and 0.9 Hz, 1H), 7.46 (m, 5H), 7.57 (br s, 1H), 7.68 (td, *J* = 7.6 and 1.8 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 8.57 (dt, *J* = 4.8 and 0.9 Hz, 1H); ^{13}C NMR δ 41.1, 52.9, 92.7, 112.9, 120.6, 121.7, 124.4, 129.0, 129.1, 129.5, 129.7, 136.3, 139.0, 143.6, 148.4, 149.2, 158.5, 170.9, 172.8] as well as **13** (308 mg, 44%) [mp 124−126 °C; IR 3065, 1725, 1585, 1493, 1324, 1131, 750, 671 cm^{-1}; ^1H NMR δ 4.02 (d, *J* = 18 Hz, 1H), 4.08 (d, *J* = 18 Hz, 1H), 7.26 (td, *J* = 6.9 and 0.9 Hz, 2H), 7.42 (m, 5H), 7.82(m, 3H), 8.01 (d, *J* = 7.9 Hz, 2H), 8.16 (dd, *J* = 7.9 and 0.9 Hz, 1H), 8.60 (dd, *J* = 5.3 and 0.9 Hz, 1H); ^{13}C NMR δ 44.5, 86.5, 118.7, 122.4, 125.0, 125.6, 126.3, 128.5, 128.9, 129.1, 131.1, 136.6, 137.5, 147.6, 149.5, 155.7, 158.0, 170.2].

3-(2-Methoxyphenyl)-7-methyl-9-(4-methylphenyl)-1-oxa-2,7,8-triazaspiro [4.4]nona-2,8-dien-6-one (14). Following general method A, **4d** (234 mg, 662 μmol) and methylhydrazine (53 μL, 1.0 mmol) in toluene gave **14** (166 mg, 72%): mp 156−157 °C; IR 3029, 2939, 2838, 1721, 1670, 1601, 1253 cm^{-1}; ^1H NMR δ 2.35 (s, 3H), 3.41 (s, 3H), 3.77 (s, 3H), 3.85 (d, *J* = 18 Hz, 1H), 3.92 (d, *J* = 18 Hz, 1H), 6.93 (d, *J* = 8 Hz, 1H), 7.01 (td, *J* = 8 and 1 Hz, 1H), 7.19 (d, *J* = 8 Hz, 2H), 7.42 (td, *J* = 8 and 2 Hz, 1H), 7.65 (d, *J* = 8 Hz, 2H), 7.89 (dd, *J* = 8 and 2 Hz, 1H); ^{13}C NMR δ 21.4, 31.8, 46.7, 55.4, 85.1, 111.4, 116.8, 120.9, 126.0, 129.6, 129.8, 132.1, 141.0, 155.3, 156.0, 157.5, 172.3. Anal. Calcd for $C_{20}H_{19}N_3O_3 \cdot 0.33H_2O$: C, 67.59; H, 5.58; N, 11.82. Found: C, 67.48; H, 5.43; N, 11.76.

3-(2-Methoxyphenyl)-7-phenyl-9-(4-methylphenyl)-1-oxa-2,7,8-triazaspiro [4.4]nona-2,8-dien-6-one (15). Following general method A, **4d** (383 mg, 1.08 mmol) and phenylhydrazine (117 μL, 1.19 mmol) in toluene gave **15** (258 mg, 58%): mp 180−181 °C; IR 3032, 2843, 1722, 1593, 1491, 1392, 1256, 756 cm^{-1}; ^1H NMR δ 2.39 (s, 3H), 3.80 (s, 3H), 3.97 (d, *J* = 18 Hz, 1H), 4.04 (d, *J* = 18 Hz, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 7.23 (m, 3H), 7.45 (m, 3H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.93 (dd, *J* = 7.9 and 1.8 Hz, 1H), 8.02 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR δ 21.5, 47.3, 55.4, 86.3, 111.5, 116.7, 118.7, 121.0, 125.4, 125.8, 126.4, 128.9, 129.7, 129.8, 132.2, 137.7, 141.6, 155.4, 156.4, 157.5, 170.7. Anal. Calcd for $C_{25}H_{21}N_3O_3$: C, 72.98; H, 5.14; N, 10.21. Found: C, 72.86; H, 5.07; N, 10.15.

3-[2-((4-Bromobenzyl)oxy)phenyl]-9-(4-methoxyphenyl)-7-methyl-1-oxa-2,7,8-triazaspiro[4.4]nona-2,8-dien-6-one (16). Following general method A, **4e** (319 mg, 608 μmol) and methylhydrazine (43 μL, 670 μmol) in toluene gave **16** (142 mg, 45%): mp 116−117 °C; IR 3080, 2954, 1721, 1681, 1601, 1258, 1173 cm^{-1}; ^1H NMR δ 3.37 (s, 3H), 3.73 (d, *J* = 18 Hz, 1H), 3.82 (s, 3H), 3.88 (d, *J* = 18 Hz, 1H), 4.98 (s, 3H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 7.03 (dd, *J* = 7.5 and 0.9 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.40 (ddd, *J* = 7.5, 1.8, and 0.9 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.85 (dd, *J* = 7.9 and 1.8 Hz, 1H); ^{13}C NMR δ 31.7, 46.5, 55.3, 69.7, 85.1, 112.5, 114.3, 117.3, 121.3, 121.5, 122.0, 127.7, 128.9, 130.3, 131.6, 132.1, 134.7, 155.4, 155.7, 156.3, 161.4, 171.9. Anal. Calcd for $C_{26}H_{22}BrN_3O_4$: C, 60.01; H, 4.26; N, 8.07. Found: C, 59.75; H, 4.33; N, 7.89.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **4a**, **9**, and **13**, X-ray structures of **3e** and the phenylhydrazone of **4c**, and tables of X-ray data for **3e**, phenylhydrazone of **4c**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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