Preparation of 2*H*-spiro[Benzo[*d*]isothiazole-3,3′-pyrazole]-1, 1-dioxide-2′(4′*H*)-carboxylates from Dilithiated *C*(α), *N*-Carboalkoxyhydrazones and Methyl 2-(Aminosulfonyl)benzoate

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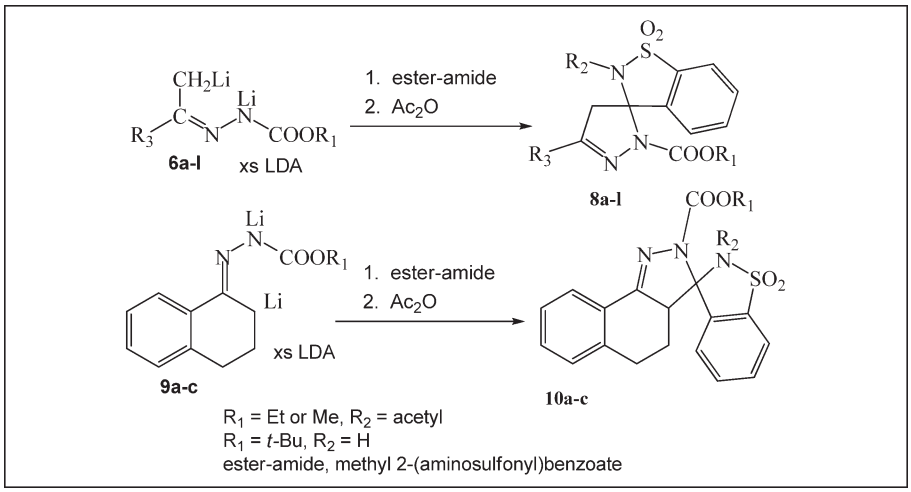

A variety of substituted spiro(benzoisothiazole-pyrazoles) have been prepared by the condensation of dilithiated *C*(α),*N*-carboalkoxyhydrazones with lithiated methyl 2-(aminosulfonyl)benzoate followed by the cyclization of intermediates with acetic anhydride, which also resulted in spiro *N*-acetylated products when carbomethoxyhydrazones or carboethoxyhydrazones were used, and spiro *NH* products when carbo-*tert*-butoxyhydrazones were used.

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INTRODUCTION

Pyrazoles [1] and benzoisothiazole dioxides [2] have been prepared and studied because of their biological potential, serving as intermediate compounds in other syntheses, spectral studies, theoretical studies, and other uses. Various spiro pyrazoles have been investigated [3], and spiro benzoisothiazoles dioxides (BIDs) have received limited study [4]. There are no reports concerning the preparation of spiro(benzoisothiazole-pyrazole) dioxides.

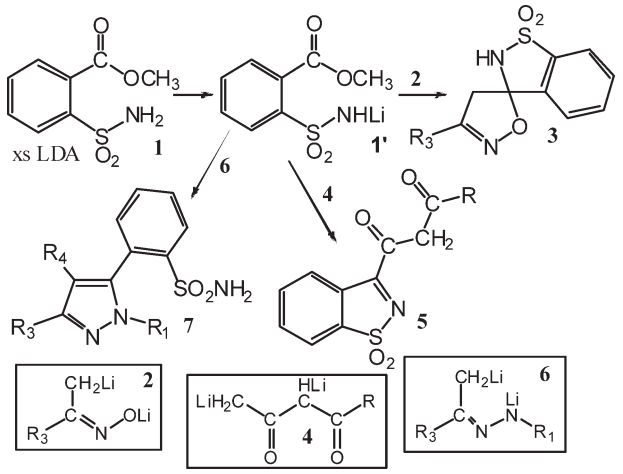
In this laboratory, BIDs and pyrazoles have been synthesized by the condensation-cyclization of polylithiated intermediates, prepared in excess lithium diisopropylamide (LDA), with methyl 2-(aminosulfonyl)benzoate **1**, Scheme 1. Specifically, anionic electrophile **1′** has been condensed-cyclized with dilithiated oximes **2** to afford spiro(BID-isoxazoles) **3** [5]; with dilithiated β-ketoesters **4** (R = OMe or OEt) to afford BID-β-ketoesters **5** (R = OMe or OEt); with dilithiated β-diketones **4** (R = Ar) to afford BID-β-diketones **5** (R = Ar); or with trilithiated β-ketoamides **4** (R = $NLiC_6H_5$) resulting in BID β-ketoamides **5** (R = NHC_6H_5) [6].

N-Phenyl-, or *NH*- pyrazolebenzenesulfonamides **7** resulted [7,8] when dilithiated phenylhydrazones (R_1 = Ph) or dilithiated carbo-*tert*-butoxyhydrazones (R_1 = *t*-Bu) were condensed-cyclized (also hydrolysis-decarboxylation for **7**, *NH*-) with **1′** (from **1**).

RESULTS AND DISCUSSION

During the current investigation dilithiated carboalkoxyhydrazones **6a–l** (**6f**, trilithiated) or **9a–c** were

Scheme 1. Condensation-cyclization syntheses with methyl 2-(aminosulfonyl)benzoate.



condensed-cyclized with lithiated methyl 2-(aminosulfonyl)benzoate **1′** (from **1**) to afford spiro(BID-pyrazoles) **8a–l** or **10a–c** and not pyrazole-benzenesulfon-amides **7** Scheme 2.

Specifically, **6a–l** or **9a–c** underwent an anion-anion condensation with **1′** to form intermediate compounds that were isolated but not characterized followed by cyclization and *N*-acetylation with acetic anhydride to afford *N*-acetyl spiro(BID-pyrazoles) **8a–f, 10a,** and **10b**. Trilithiated 2′-hydroxyacetophenone carbomethoxy-hydrazone **6f** (R_3 = 2-$LiOC_6H_4$) was condensed with **1′**, and intermediates were cyclized to afford *O*-acetylation and *N*-acetylation spiro product **8f**. The *N*-acetylation process did not occur when dilithiated carbo-*tert*-butoxy-hydrazone intermediates were used instead, and only *NH* spiro(BID-pyrazoles) **8g–l** and **10c** were isolated.

N-Acetylated spiro(BID-pyrazoles) **8a–f** were not originally anticipated, and an X-ray single crystal analysis was determined for spiro product **8a** resulting from the condensation-cyclization of **6a** (R_1 = Et, R_3 = C_6H_5) with **1′**.

The molecular structure of **8a** is shown in Figure 1 (atoms assigned numbers), and selected bond distances and angles are listed in Table 1. The bond lengths agree with the assignment of the double bond shown between C9 and N2. Because the unit cell of each compound is centrosymmetric, both enantiomorphic structures about the C1 chiral center are present.

The least squares best planes representing the fused rings are nearly coplanar with angles of 1.52° between

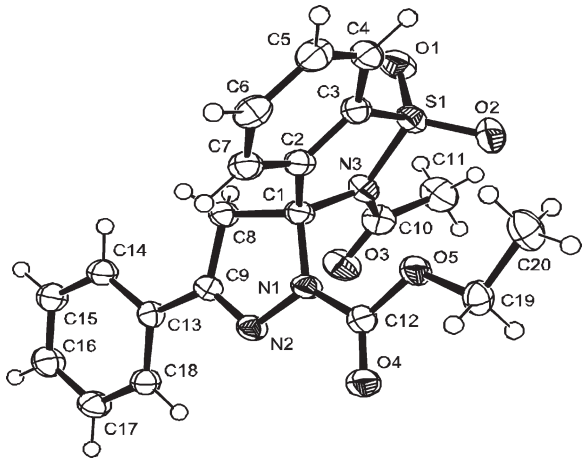
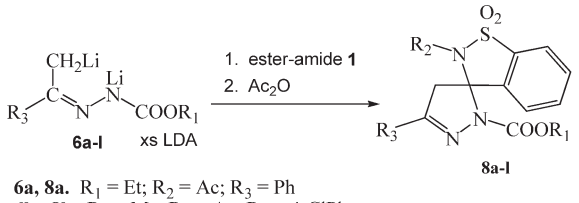
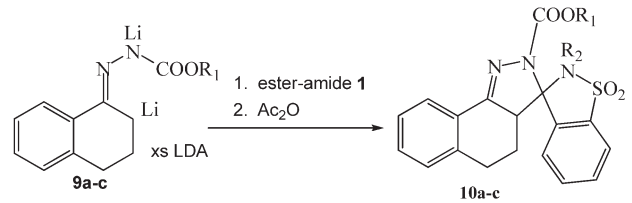


Figure 1. ORTEP diagram (50% ellipsoids for non-hydrogen atoms), $C_{20}H_{19}N_3O_5S$ **8a** [9].

Scheme 2. Reactants/products.



6a, 8a. R_1 = Et; R_2 = Ac; R_3 = Ph
6b., 8b. R_1 = Me; R_2 = Ac; R_3 = 4-ClPh
6c., 8c. R_1 = Me; R_2 = Ac; R_3 = 2-furanyl
6d., 8d. R_1 = Et; R_2 = Ac; R_3 = 2-furanyl
6e., 8e. R_1 = Me; R_2 = Ac; R_3 = 4-MePh
6f., 8f. R_1 = Me; R_2 = Ac; R_3 = 2-acetoxyPh
6g., 8g. R_1 = *t*-Bu; R_2 = H; R_3 = 4-MeOPh
6h., 8h. R_1 = *t*-Bu; R_2 = H; R_3 = 3,4-diMeOPh
6i., 8i.. R_1 = *t*-Bu; R_2 = H; R_3 = Ph
6j., 8j. R_1 = *t*-Bu, R_2 = H; R_3 = 4-MePh
6k., 8k. R_1 = *t*-Bu; R_2 = H; R_3 = 4-ClPh
6l., 8l. R_1 = *t*-Bu; R_2 = H; R_3 = 3,4-diMePh



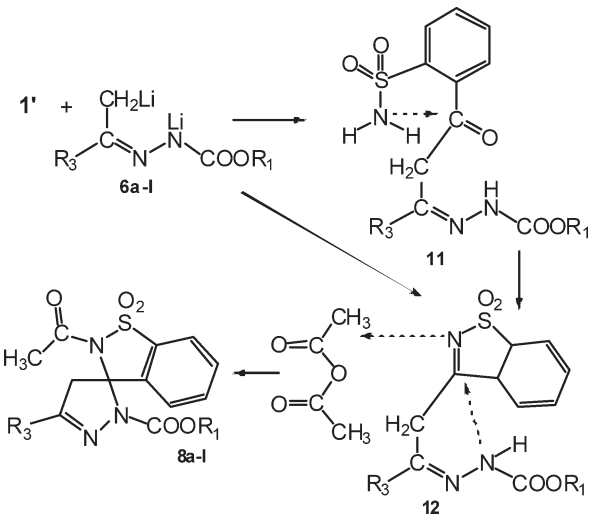
9a.,10a. R_1 = Et; R_2 = Ac
9b.,10b. R_1 = Me; R_2 = Ac
9c., 10c. R_1 = *t*-Bu; R_2 = H

Table 1

Selected bond distances (Å) and angles (°), $C_{20}H_{19}N_3O_5S$ **8a**.

C1-C2	1.524(3)	C1-C2-C3	115.4(2)
C2-C3	1.376(3)	C2-C3-S1	112.0(2)
C3-S1	1.742(2)	C3-S1-N3	92.8(1)
S1-N3	1.690(2)	S1-N3-C1	115.6(1)
N3-C1	1.491(3)	N3-C1-C2	104.1(2)
C1-N1	1.475(2)	C1-C8-C9	103.1(2)
N1-N2	1.399(2)	C8-C9-N2	114.0(2)
N2-C9	1.288(3)	C9-N2-N1	107.8(2)
C9-C8	1.500(3)	N2-N1-C1	113.7(2)
C8-C1	1.550(3)	N1-C1-C8	100.5(2)
C9-C13	1.472(3)	C14-C13-C9-N2	172.8(2)
N1-C12	1.371(3)	C13-C9-N2-N1	176.8(2)
C12-O4	1.206(3)	N2-N1-C12-O4	−4.1(3)
C12-O5	1.342(3)		

Scheme 3. Mechanistic Details.



them. The two five-member rings in each molecule are nearly perpendicular with an angle of 89.54°. The rings connected by C9 and C13 are nearly coplanar with angles of 9.19°, which allows for extended pi bonding between these rings and possibly with the atoms in the C12 carboxylate group.

In addition to single crystal X-ray analysis leading to results illustrated in the ORTEP diagram, Figure 1, other representative characterization parameters supported the spiro structure, such as DEPT clearly identifying CH_2 or CH in appropriate products. The ^{1}H-NMR CH_2 absorption for **8a–l** were noted as a pair of doublets δ 3.54–3.66 and δ 3.97–4.04 ppm, J = 18.0–18.7 Hz; *N*-acetyl singlet proton absorptions were displayed at δ 2.52–2.64, usually 2.63 or 2.64 ppm in products **8a–f**, **10a** and **10b** and absent in products **8g–l** and **10c**. The ^{13}C NMR for all products displayed the spiro carbon absorption from δ 80.4–84.0 ppm. Combustion analysis indicated incorporation of water (methanol in **8k**) [10] in the analytical crystalline products **8a, 8c, 8d, 8j,** and **8l**. LCMS for most of the products contained the expected $(M + H)^+$; for **8i** and **8j** it was not detected. Base ions for each of these products may be explained by loss of a carbo-*tert*-butoxy fragment.

Mechanistic details, Scheme 3, to explain the formation of products may involve dilithiated carboalkoxyhydrazone and monolithiated ester-sulfonamide **1′**, leading to intermediates **11** and/or **12** (*e.g.,* from acetophenones), with each having potential for difficulty in cyclodehydration. Attempts to isolate saccharin from treatment of **1** (to **1′**) with LDA under the same reaction conditions were unsuccessful.

Products **8g–l** and **10c** were only formed from cyclization and not accompanied by *N*-acetylation, which may be attributed to the larger size of the *tert*-butoxy group hindering further reaction at the BIDs nitrogen with acetic anhydride, and its success was dependant on the strong cyclization ability of acetic anhydride/pyridine.

EXPERIMENTAL

Melting points were obtained with a Mel-Temp II melting point apparatus in open capillary tubes and are uncorrected. Entry compounds, *C*(α),*N*-carboalkoxy-hydrazones were prepared from *C*(α),*O*-ketones in a 1:1 condensation with methyl, ethyl, or *tert*-butyl carbazate [11]. The tetrahydrofuran (THF) was distilled from sodium (benzophenone ketyl as an indicator of dryness) prior to use, and organic chemicals were obtained from Aldrich Chemical Co. Infrared spectra were obtained with a Nicolet Impact 410 FT-IR. Proton and ^{13}C NMR spectra were obtained with a Varian Associates Mercury Oxford 300 MHz nuclear magnetic resonance spectrometer, and chemical shifts were recorded in δ ppm downfield from an internal tetramethylsilane standard. Combustion analyses were performed by Quantitative Technologies, Inc., P.O. Box 470, Whitehouse, NJ 08888. LCMS analyses were measured on a Thermo-Finnigan LCQ Advantage system with the Surveyor autosampler, Surveyor pump, and LCQ Advantage Max mass spectral detector using electrospray ionization; 2 mg samples were prepared in 2 mL/L of acetonitrile; 10 μL injections were pumped at 1.00 mL/min isocratically with 70% acetonitrile and 30% water, each buffered with 0.1% formic acid by volume; 15 min runs were reproduced in both the positive and negative (when needed) MS modes. Data were collected at full scan from 100 to 650 amu.

2*H*-spiro[Benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylates (8a–l) and (10a–c). LDA (0.0788 mol or 0.0945 mol for **8f**) was prepared by the addition of 49 mL (or 59 mL for **8f**) of 1.6*M* *n*-butyllithium in hexanes to a three-neck round-bottomed flask (*e.g.*, 500 mL), equipped with a nitrogen inlet tube, a side-arm addition funnel (*e.g.*, 125 mL), and a magnetic stir bar. The flask was cooled in an ice water bath and 8.02 g or 9.54 g for **8f** (0.0788 mol or 0.0945 mol for **8f**) of diisopropylamine, dissolved in 25–30 mL of dry THF, was added from the addition funnel at a fast dropwise rate during a 5 min period (0°C, nitrogen). The solution was stirred for an additional 15–20 min, and then 0.0150 mol of the carboalkoxyhydrazone dissolved in 50 mL of THF was added at a fast dropwise rate during 5–10 min. After 1 hr (2 h for **8f**), 3.39 g (0.0158 mol) of methyl 2-(aminosulfonyl)benzoate **1**, dissolved in 25-35 mL of THF was added, during 5 min, to the polylithiated intermediate, and the solution was stirred and condensed for 1 h. Finally, 100 mL of 3*M* hydrochloric acid was added quickly followed by 100 mL of solvent grade ether, then stirring the two-phase mixture for 5 min, followed by careful neutralization with solid sodium bicarbonate, and the two liquid phases or solid materials separated. If a solid appeared at this point, the biphasic mixture could be filtered. The aqueous layer was extracted with ether or THF (2 × 75 mL), and the organic fractions were combined, filtered, evaporated, and the solid organic materials were air-dried.

The twofold cyclization and acetylation required 6 mL of acetic anhydride and 4 mL of pyridine for each 1 g of dry intermediate(s) compound(s) [12]. Each gram of solid inter-

mediate(s) was dissolved in pyridine followed by the dropwise addition of acetic anhydride. The solution was stirred at room temperature for 1 h. The addition of *ca.* 80 g of ice usually resulted in a precipitate, which was collected by filtration, washed with water and recrystallized from methanol or ethanol.

Ethyl2-acetyl-5′-phenyl-2*H*-spiro[benzo-[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8a). Compound **8a** was obtained in 69% yield, mp 179–182°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated acetophenone carboethoxyhydrazone and **1′**. IR: 1709 and 1727 cm^{-1}. ^1H NMR (deuteriochloroform): δ 1.67 (m, 3H), 2.64 (s, 3H, CH_3), 3.68–4.06 (m, 4H) [13], and 7.41–7.68, 7.71–7.91 (m, 9H, ArH). ^{13}C NMR (deuteriochloroform): δ 14.8, 23.7, 49.5 (DEPT CH_2), 53.6, 81.2, 121.2, 122.9, 127.6, 128.9, 129.2, 131.3, 132.5, 133.5, 135.3, 137.1, 147.7, 151.0 and 166.9. LCMS, exact mass, 413.10: $(M + H)^+$, 414.04. *Anal.* Calcd for $C_{20}H_{19}N_3O_5S \cdot 1/4\ H_2O$: C, 57.47; H, 4.70; N, 10.05. Found: C, 57.47; H, 4.63; N, 10.08.

Single crystal X-ray structure determination. Yellow crystals of $C_{20}H_{19}N_3O_5S$ **8a** were recrystallized from ethanol in order to give satisfactory crystals for X-ray determination. Crystal data for X-ray studies were collected at −120°C on a Mercury CCD area detector coupled with a Rigaku AFC8 diffractometer with graphite monochromated Mo-K radiation. Data were collected in 0.50° oscillations in ω with 20 s exposures. A sweep of data was done using ω oscillations from −40.0° to 90.0° at χ = 45.0° and φ = 0.0°; a second sweep was performed using ω oscillations from −30.0° to 80.0° at χ = 45.0° and φ = 90.0°. The crystal-to-detector distances were 27.7147 mm. Details of the data collection is reported in Table 2. Data were collected, processed, and corrected for Lorentz polarization and for absorption using CrystalClear (Rigaku) [15].

The non-hydrogen atoms were refined anisotropically. Ideal hydrogen atom coordinates were calculated and the hydrogen atoms were allowed to ride on their respective carbon atoms. The temperature factors of all hydrogen atoms were varied isotropically. Structure solution, refinement, and the calculation of derived results were performed using the *SHELX-97* [16] package of computer programs. Neutral atom scattering factors were those of Cromer and Waber [16], and the real and imaginary anomalous dispersion corrections were those of Cromer [17].

Table 2

Crystallographic data, $C_{20}H_{19}N_3O_5S$ **8a**.

CCDC deposit number [17]	689213
Color/shape	Yellow/Parallelopiped
Crystal dimensions (mm)	0.36 × 0.36 × 0.31
Formula	$C_{20}H_{19}N_3O_5S$
Formula mass	413.44
T (°C)	−120(2)
Crystal system	Monoclinic
Space Group	$P2_1/c$
a (Å)	12.372(3)
b (Å)	17.490(4)
c (Å)	9.655(2)
β (°)	107.12(3)
V ($Å^3$)	1996.6(7)
Z	4
d_{calc} (g cm^{-3})	1.375
λ (Å)	0.71073
μ (mm^{-1})	0.199
F(000)	864
θ range (°)	3.45–25.15
Reflections collected	3952
Miller indices	$-14 \le h \le 14$, $0 \le k \le 20$, $0 \le l \le 11$
Unique reflections	3,544
Unique reflections $I > 2\sigma(I)$	3,121
Max and min transmission	0.9408, 0.9317
Data, restraints, parameters	3544, 0, 264
Final *R* indices $I > 2\sigma(I)$	$R_1 = 0.0515$
	$wR_2 = 0.1243$
R indices all data	$R_1 = 0.0585$
	$wR_2 = 0.1305$
Goodness of fit on F^2	1.098
Largest diff peak and hole (e $Å^{-3}$)	0.245, −0.373

Methyl 2-acetyl-5′-(4-chlorophenyl)-2*H*-spiro-[benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8b). Compound **8b** was obtained in 74% yield, mp 181°C dec (benzene/hexanes), from the two-step procedure for the condensation-cyclization of dilithiated 4′-chloroacetophenone carbomethoxyhydrazone and **1′**. IR: 1705 cm^{-1}. ^1H NMR (deuteriochloroform): δ 2.64 (s, 3H, CH_3), 3.67(d, 1H, *J* = 18.7 Hz), 3.74 (s, 3H, CH_3O), and 3.99 (d, 1H) and 7.39–7.50, 7.68–7.82 (m, 7H, ArH) and 7.90 (d, 1H, *J* = 7.5 Hz). ^{13}C NMR (deuteriochloroform): δ 24.0, 49.0 (DEPT CH_2), 53.9, 81.6, 121.5, 123.1, 128.2, 129.3, 131.6, 132.7, 135.6, 136.9, 151.1. LCMS, exact mass, 433.05: $(M + H)^+$, 433.99; $(M - H)^-$, 432.10. *Anal.* Calcd for $C_{19}H_{16}$ Cl N_3O_5S: C, 52.60; H, 3.72; N, 9.69. Found: C, 52.75; H, 3.64; N, 9.70.

Methyl 2-acetyl-5′-(2-furanyl)-2*H*-spiro-[benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8c). Compound **8c** was obtained in 44% yield, mp 177–178°C (benzene/hexanes), from the two-step procedure for the condensation-cyclization of dilithiated 2-acetylfuran carbomethoxyhydrazone and **1′**. IR: 1709 and 1728 cm^{-1}. ^1H NMR (deuteriochloroform): δ 2.64 (s, 3H, CH_3), 3.66 (d, 1H, *J* = 18.6 Hz), 3.74 (s, 3H, CH_3O), 3.97 (d, 1H, *J* = 18.6 Hz), 6.51–6.53 (m, 1H), 6.87 (s br, 1H), 7.47–7.54 (m, 1H), 7.69–7.83 (m, 3H, ArH) and 7.89 (d, 1H, *J* = 7.5 Hz). ^{13} C NMR (deuteriochloroform): δ 23.9, 48.6 (DEPT CH_2), 53.7, 80.9, 112.2, 112.7, 121.4, 123.0, 131.5, 132.6, 135.5, 137.2, 144.0, 144.9, 145.8, 151.2, and 167.0. LCMS exact mass, 389.07: $(M + H)^+$, 389.94. *Anal.* Calcd for $C_{17}H_{15}N_3O_6S \cdot 1/2\ H_2O$: C, 51.25; H, 4.05; N, 10.55. Found: C, 51.30; H, 3.91; N, 10.33.

Ethyl 2-acetyl-5′-(2-furanyl)-2*H*-spiro-[benzo[*d*]-isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8d). Compound **8d** was obtained in 40% yield, mp 145–147 °C (ethanol), from the two-step procedure for the condensation-cyclization of dilithiated 2-acetylfuran carboethoxyhydrazone and **1′**. IR: 1712 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.06 (t, 3H), 2.50 (s, 3H), 3.43–3.46 (m, 1H), 3.88–3.96 (m, 3H), 6.67–6.69 (m, 1H), 6.94 (d, 1H, *J* = 3.6 Hz), 7.76–7.92 (m, 5H), and 8.14 (d, 1H, *J* = 7.8 Hz). ^{13}C NMR (DMSO-d_6): δ 23.4, 48.1, 61.7, 80.8, 112.2, 113.6, 121.0, 123.9, 131.6, 135.8, 143.9, 145.6, and 166.1. LCMS, exact mass, 403.08: $(M + H)^+$, 403.95; $(M - H)^-$, 402.11. *Anal.* Calcd for $C_{18}H_{17}N_3O_6S \cdot 7/8\ H_2O$: C, 51.58; H, 4.51; N, 10.02. Found: C, 51.48; H, 3.38; N, 9.95.

Methyl 2-acetyl-5′-(4-methylphenyl)-2*H*-spiro-[benzo[*d*]-isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8e). Compound **8e** was obtained in 40% yield, mp 166–168°C (methanol), from the two-step procedure for the

condensation-cyclization of dilithiated 4′-methylacetophenone carbomethoxyhydrazone and **1′**. IR: 1709 and 1728 cm^{-1}. ^1H NMR (deuteriochloroform): δ 2.39 (s, 3H), 2.63 (s, 3H), 3.65–4.03 (m, 5H) [13], 7.21–7.28, 7.46–7.48, and 7.63–7.90 (m, 8H). ^{13}C NMR (DMSO-d_6): δ 21.7, 24.1, 48.9 (DEPT CH_2), 53.4, 82.0, 121.4, 124.5, 127.4, 128.5, 130.0, 132.2, 136.4, 137.5, 140.1, 151.2, 153.1, and 166.7. LCMS, exact mass, 413.10: $(M + H)^+$, 414.08. *Anal*. Calcd for $C_{20}H_{19}N_3O_5S$: C, 58.10; H, 4.63; N, 10.16. Found: C, 58.06; H, 4.70; N, 9.97.

Methyl 2-acetyl-5′-(2-acetoxyphenyl)-2*H*-spiro-[benzo[*d*]-isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8f). Compound **8f** was obtained in 58% yield, mp 218–220°C (benzene/hexanes) from the two-step procedure for the condensation-cyclization of trilithiated 2′-hydroxyacetophenone carbomethoxyhydrazone and **1′**. IR: 1703 and 1728 cm^{-1}. ^1H NMR (deuteriochloroform): δ 2.39 (s, 3H), 2.63(s, 3H), 3.65–3.71 (m, 4H), 4.02 (d, 1H, J = 18.3 Hz), 7.18 (d, 1H, J = 7.8 Hz), 7.26–7.31 (m, 1H), 7.42–7.49 (m, 2H), 7.69–7.80 (m, 3H), and 7.87 (d, 1H, J = 7.8 Hz). ^{13}C NMR (deuteriochloroform): δ 22.3, 23.8, 50.2, 53.4 (DEPT CH_2), 80.6, 121.2, 123.0, 123.3, 124.9, 126.3, 129.5, 131.4, 132.5, 135.5, 137.2, 148.8, 149.0, 151.1, 166.9, and 170.1. LCMS, exact mass, 457.09: $(M + H)^+$, 457.93. *Anal*. Calcd for $C_{21}H_{19}N_3O_7S$: C, 58.10; H, 4.63; N, 10.16. Found: C, 58.06; H, 4.70; N, 9.97.

1,1-Dimethylethyl 5′-(4-methoxyphenyl)-2*H*-spiro-[benzo-[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8g). Compound **8g** was obtained in 92% yield, mp 190–191°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated 4′-methoxyacetophenone carbo-*t*-butoxyhydrazone and **1′**. IR: 1696 and 3128 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.03 (s, 9H, CH_3), 3.68–3.91 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 7.04 (d, 2H, J = 9.0 Hz), 7.63–7.88 (m, 6H), and 9.18 (s, NH). ^{13}C NMR (DMSO-d_6): δ 27.2, 49.3 (DEPT CH_2), 55.4, 80.6, 80.9, 114.2, 120.6, 123.5, 123.9, 128.2, 130.3, 133.6, 135.5, 139.8, 149.9, 151.3, and 160.8. LCMS, exact mass, 429.14: $(M + H)^+$, 429.67. *Anal*. Calcd for $C_{21}H_{23}N_3O_5S$: C, 58.73; H, 5.40; N, 9.78. Found: C, 58.41; H, 5.49; N, 9.65.

1,1-Dimethylethyl 5′-(3,4-dimethoxyphenyl)-2*H*-spiro-[benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8h). Compound **8h** was obtained in 38% yield, mp 200–203°C (ethanol), from the two-step procedure for the condensation-cyclization of dilithiated 3′,4′-dimethoxyacetophenone carbo-*t*-butoxyhydrazone and **1′**. IR: 1727 and 3231 cm^{-1}. ^1H NMR (deuteriochloroform): δ 1.17 (s, 9H, CH_3), 3.65 (d, 1H, J = 15.0 Hz), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.95 (d, 1H, J = 18.3 Hz), 6.81 (d, 1H, J = 8.4 Hz), 7.01 (dd, 1H, J = 8.1 Hz), 7.39 (d, 1H, J = 2.1 Hz), 7.51 (d, 1H, J = 7.8 Hz), 7.61–7.74 (m, 2H), and (7.81 and 7.83 singlets broad, 1H). ^{13}C NMR (deuteriochloroform): δ 27.8, 50.5 (DEPT CH_2), 81.3, 83.4, 108.6, 110.6, 120.7, 121.3, 123.9, 123.3, 130.5, 133.9, 136.1, 141.3, 149.1, 150.3, 151.3, and 151.6. LCMS, exact mass, 459.15: $(M + H)^+$, 459.64. *Anal*. Calcd for $C_{22}H_{25}N_3O_6S$: C, 57.50; H, 5.48; N, 9.14. Found: C, 57.26; H, 5.55; N, 9.03.

1,1-Dimethylethyl 5′-phenyl-2*H*-spiro-[benzo[*d*]-isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8i). Compound **8i** was obtained in 59% yield, mp 193–197°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated acetophenone carbo-*t*-butoxyhydrazone and **1′**. IR: 1701, 1728, and 3195 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.25 (s, 9H, CH_3), 3.66 (d, 1H, J =18.3 Hz), 4.04 (d, 1Hz, J = 18.3 Hz), 5.78 (s, 1H), and 7.39–7.41, 7.61–7.82 (m, 9H). ^{13}C NMR (deuteriochloroform): δ 27.7, 50.5 (DEPT CH_2), 81.4, 83.6, 121.1, 122.8, 126.8, 128.3, 128.8, 130.2, 130.4, 130.7, 133.8, 136.2, and 151.9. LCMS, exact mass, 399.13: LCMS, $(M + H)^+$ not detected, base peak 299.07. *Anal*. Calcd for $C_{20}H_{21}N_3O_4S$: C, 60.13; H, 5.30; N, 10.52. Found: C, 59.98; H, 5.37; N, 10.50.

1,1-Dimethylethyl 5′-(4-methylphenyl)-2*H*-spiro-[benzo-[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8j). Compound **8j** was obtained in 33% yield, mp 181.5–182°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated 4′-methylacetophenone carbo-*t*-butoxyhydrazone and **1′**. IR: 1697 and ∼3100 broad cm^{-1}. ^1H NMR (deuteriochloroform): δ 1.17 (s, 9H, CH_3), 2.37 (s, 3H, CH_3), 3.62 (d, 1H, J = 18.0 Hz), 3.99 (d, 1H, CH_3, J = 18.0 Hz), 5.84 (s), 7.20 (d, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 7.8 Hz), 7.59–7.72 (m, 5H), and 7.81 (d, 1H, J = 7.8 Hz). ^{13}C NMR (deuteriochloroform): δ 21.7, 27.8, 50.7, 81.5, 83.6, 121.3, 123.0, 127.0, 127.4, 127.6, 129.7, 130.5, 133.8, 136.3, 141.4, 141.7, 150.3, and 152.1. LCMS, exact mass, 413.14: $(M + H)^+$ not detected, base peak 314.00. *Anal*. Calcd for $C_{21}H_{23}N_3O_5S \cdot 1/4\ H_2O$: C, 60.34; H, 5.67; N, 10.05. Found: C, 60.28; H, 5.70; N, 10.05.

1,1-Dimethylethyl 5′-(4-chlorophenyl)-2*H*-spiro-[benzo-[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (8k). Compound **8k** was obtained in 35% yield, mp 152–155°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated 4′-chloroacetophenone carbo-*t*-butoxyhydrazone and **1′**. IR: 1693 and 3438 broad cm^{-1}. ^1H NMR (deuteriochloroform): δ 1.15 (s, 9H), 3.54 (d, 1H, J = 18.0 Hz), 4.00 (d, 1H, J = 18.3 Hz), 7.38 (d, 2H, J = 8.7 Hz), 7.49 (d, 1H, J = 7.5 Hz), 7.63–7.70 (m, 4H), and 7.79 (d, 1H, J = 6.9 Hz). ^{13}C NMR (deuteriochloroform): δ 27.9, 50.6, 51.0, 81.7, 83.9, 121.5, 123.1, 128.3, 129.1, 129.4, 130.7, 134.1, 136.3, 137.0, 141.3, 150.4, and 151.1. LCMS, exact mass, 433.09: $(M + H)^+$, 433.75. *Anal*. Calcd for $C_{20}H_{20}\ Cl\ N_3O_4S \cdot 5/4\ CH_3OH$ [10]: C, 53.74; H, 5.52; N, 8.85. Found: C, 53.88; H, 5.19; N, 8.94.

1,1-Dimethylethyl 5′-(3,4-dimethylphenyl)-2*H*-spiro-[benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-car-boxylate (8l). Compound **8l** was obtained in 31% yield, mp 197–201°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated 3′,4′-dimethylacetophenone carbo-*t*-butoxyhydrazone and **1′**. IR: 1712 and 3415 cm^{-1}. ^1H NMR (deuteriochloroform): δ 1.18 (s, 9H, CH_3), 2.28 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.64 (d, 1H, J = 18.3 Hz), 4.01(d, 1H, CH_3, J = 18.0 Hz), 5.7 (s), 7.17 (d, 1H, J = 8.1 Hz), 7.42–7.59 (m, 2H), 7.60–7.73 (m, 4H), and 7.81 (d, 2H, J = 7.8 Hz). ^{13}C NMR (deuteriochloroform): δ 19.7, 19.9, 27.7, 50.7 (DEPT CH_2), 81.3, 83.4, 107.4, 121.1, 122.8, 124.4, 127.7, 127.9, 130.0, 130.3, 133.8, 136.2, 137.2, 140.0, and 152.2. LCMS, exact mass, 427.16: $(M + H)^+$, 427.70. *Anal*. Calcd for $C_{22}H_{25}N_3O_4S \cdot 1H_2O$: C, 59.31; H, 6.11; N, 9.43. Found: C, 59.69: H, 6.26; N, 9.07.

Ethyl 2-acetyl-3′-(4,5-dihydrobenz[*g*]indazinyl)-2*H*-spiro-[benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (10a). Compound **10a** was obtained in 60% yield, mp 257–259°C dec (methanol), from the two-step procedure for the condensation-cyclization of dilithiated 1-tetralone carboethoxyhydrazone and **1′**. IR: 1703 and 1739 cm^{-1}. ^1H NMR

(deuteriochloroform): δ 0.91 (m, 1H), 1.27 (m, 3H), 1.80–1.84 (m, 1H), 2.03–2.05 (m, 1H), 2.52 (s, 3H, CH_3), 3.70–3.91 (m, 3H, OCH_3), 7.16–7.18 (m, 1H), 7.29–7.37 (m, 3H), 7.61–7.90 (m, 4H), and 8.22–8.24 (m, 1H). ^{13}C NMR (deuteriochloroform): δ 14.3, 22.1 (DEPT CH_2), 24.1 (CH_3 DEPT), 29.5 (CH_2 DEPT), 59.1 (DEPT CH), 62.9, 84.0, 121.4, 123.4, 125.9, 126.4, 127.2, 129.2, 131.0, 131.3, 132.6, 135.3, 138.9, 152.9, and 167.6. LCMS, exact mass, 439.12: $(M + H)^+$, 439.99. *Anal*. Calcd for $C_{22}H_{21}N_3O_5S$: C, 60.12; H, 4.82; N, 9.56. Found: C, 59.82; H, 4.54; N, 9.95.

Methyl 2-acetyl-3′-(4,5-dihydrobenz[*g*]indazinyl)-2*H*-spiro[benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-di-oxide-2′(4′*H*)-carboxylate (10b). Compound **10b** was obtained in 71% yield, mp 209°C dec (ethanol), from the two-step procedure for the condensation-cyclization of dilithiated 1-tetralone carbomethoxyhydrazone and **1′**. IR: 1701 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 1.80–1.85 (m, 1H), 2.03–2.06 (m, 1H), 2.63 (s, 3H, CH_3), 2.75–2.98 (m, 2H), 3.60–3.82 (m, 4H, CH and OCH_3), 7.16–7.39, 7.57–7.90 (m, 7H), and 8.21 (d, 1H, J = 6.6 Hz). ^{13}C NMR (deuteriochloroform): δ 22.1, 24.1, 29.5, 53.9 (DEPT CH_2), 59.2, 84.0, 121.5, 123.3, 125.8, 127.3, 129.2, 131.1, 131.4, 131.7, 132.7, 135.4, 139.1, 152.0, 153.2, and 167.8. LCMS, exact mass, 425.10: $(M + H)^+$, 426.05. *Anal*. Calcd for $C_{21}H_{19}N_3O_5S$: C, 59.28; H, 4.50; N, 9.88. Found: C, 58.94; H, 4.63; N, 9.60.

1,1-Dimethylethyl 3′-(4,5-dihydrobenz[*g*]indazinyl)-2*H*-spiro[benzo[*d*]isothiazole-3,3′-pyrazole]-1,1-dioxide-2′(4′*H*)-carboxylate (10c). Compound **10c** was obtained in 39 % yield, mp 187–188°C (methanol), from the two-step procedure for the condensation-cyclization of dilithiated 1-tetralone carbo-*t*-butoxyhydrazone and **1′**. IR: 1689 and 3183 broad cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.05 (s, 9H, CH_3), 1.70–1.74 (m, 1H of CH_2), 1.91–1.99 (m, 1H of CH_2), 2.69–3.00 (m, 2H, CH_2), 3.85 (dd, 1H, CH, J = 4.4, 13.2 Hz), 7.29–7.42 (m, 3H), and 7.67–7.92 (m, 4H), 7.93 (d, 1H, J = 7.2 Hz), and 9.27 (s, NH). ^{13} C NMR (DMSO-d_6): δ 21.9, 27.8, 28.9, 56.3 (DEPT CH), 81.3, 83.9, 121.2, 124.5, 124.7, 127.47, 127.52, 129.9, 139.9, 131.1, 133.9, 136.3, 139.9, 140.2, 150.9, and 153.0. LCMS, exact mass, 425.14: $(M + H)^+$, 425.74. *Anal*. Calcd for $C_{22}H_{23}N_3O_4S$: C, 62.10; H, 5.45; N, 9.88. Found: C, 62.14; H, 5.52; N, 9.78.

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