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One-Pot Synthesis of Functionalized Spirobenzofuranones via MCR involving 3-Cyanochromones

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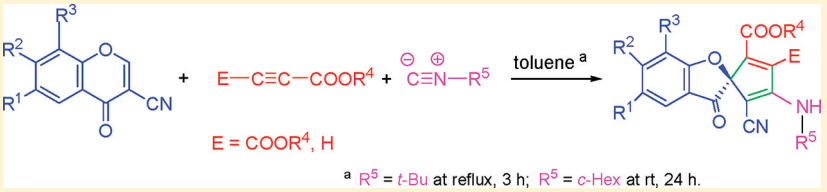
Supporting Information



ABSTRACT: Another aspect concerning chromone chemistry leading to the one-pot synthesis of functionalized novel spirobenzofuranones has been described. The synthesis involves reaction of the zwitterionic intermediates formed by the 1:1 interaction between isocyanides and acetylenecarboxylates with 3-cyanochromones, whereupon through an unexpected and unprecedented reaction of the chromone moiety the isolated benzofuranones are formed. The regioselectivity of the reaction was investigated by DFT calculations. The geometries of the intermediates, transition structures, and intermediate products, leading to the final products, were optimized using the B3LYP functional with the 6-31G(d) basis set. The structures of the products were elucidated by 1D and 2D NMR experiments. Full assignment of all ^{1}H and ^{13}C NMR chemical shifts has been achieved. A plausible mechanistic rationale is proposed.

INDRODUCTION

Carbon−carbon and carbon−heteroatom bond-forming reactions are central to organic synthesis. Despite the enormous progress made during the last few decades in the application of polar, pericyclic, and radical reactions in such bond construction, there is the perennial quest to discover newer and simpler reactions in this area. Polar reactions customarily utilize a variety of reactive intermediates in these types bond-forming reactions. In this context, among the plethora of methods available for heterocyclic construction, the generation of zwitterionic species and their trapping by suitable π-systems leading to five-membered heterocycles occupies a prime position, attributable in a large measure to the monumental contributions of Huisgen.[1]

Derivatives of 4*H*-1-benzopyran-4-one, also known as 4*H*-chromen-4-ones or chromones, are important natural products possessing wide range of valuable physiological activities.[2] The chromone moiety is also part of pharmacophores of various biologically active molecules[3,4] including anticancer agents such as psorospermin and pluramycin A.[5,6] Concerning 3-cyano-4-benzopyrones, the introduction of an electron-withdrawing group at the 3-position of the chromone system changes crucially the reactivity of the pyrone ring and provides a broad synthetic potential in organic[7] and medicinal[8] chemistry. As a result, 3-cyano-4-benzopyrones are important intermediates not only in the synthesis of therapeutically useful antiallergic drugs such as amlexanox[8a] but also in the synthesis of benzopyranopyridines with antiarthritic activity.[8b] They are also reported as useful dienophiles in [4 + 2] cycloaddition reactions and in the construction of the tricyclic ring of arisugacin, which is a selective inhibitor of acetylcholinesterase.[8c]

Against this literature background, and being well-known that multicomponent reactions (MCRs) involving isocyanides are among the more versatile reactions[9] in terms of scaffolds and number of accessible compounds, we sought to establish a new reaction by trapping the zwitterionic intermediates, derived from acetylenecarboxylates and isocyanides, with 3-cyanochromones aiming at the formation of novel heterocyclic systems, thus extending our contribution to chromone chemistry.[10] Indeed, instead of the expected fused cyclopentadienochromone derivatives, novel spirobenzofuranones were isolated. It is worth mentioning that spirocyclic systems constitute a very interesting class of compounds[11] found in a wide variety of natural products.[12] In this context, a number of synthetic methods have been devised for the synthesis of this structural motif.[13] Among them, the spirocyclic benzofurans have attracted considerable attention[14] because of their biological properties. For example, griseofulvin, still in clinical use today,[15] has been long known for its antifungal properties,[16] whereas recently has received renewed attention due to reports of both antiproliferative effects in cancer cells[17] as well as suppression of hepatitis C replication.[18]

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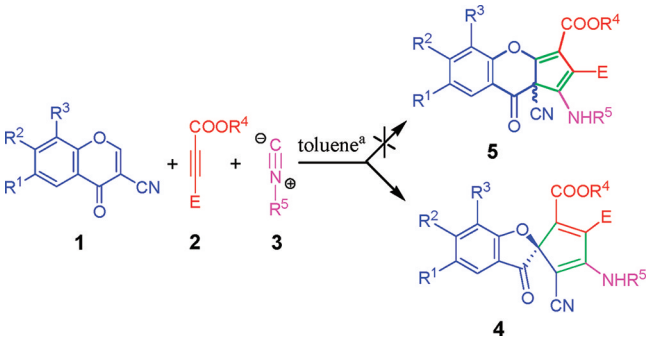
RESULTS AND DISCUSSION

Our initial experiments were focused on the reaction of *tert*-butyl isocyanide and dimethyl acetylenedicarboxylate with 3-cyanochromone. Indeed, upon treatment of 3-cyanochromone with dimethyl acetylenedicarboxylate in the presence of *tert*-butylisocyanide in a 1:1.2:1.2 molar ratio, in 20 mL of toluene at room temperature for 24 h, the reaction afforded the spirobenzofuranocyclopentadiene **4a** as the sole product in low yield (15%), instead of the expected cycloaddition product **5a** (Scheme 1). Since a substantial amount of the starting material

Scheme 1. Reaction of 3-Cyanochromones with Isocyanides and Acetylenecarboxylates



[a]In the case of R^5 = *t*-Bu at reflux for 3 h; in the case of R^5 = *c*-Hex at rt for 24 h.

was recovered unchanged, the reaction was repeated at 40 °C, whereupon the yield was improved substantially and the same product **4a** was obtained in 26% yield (Table 1), along with

Table 1. Effect of the Reaction Conditions on the Product Yield

entry	solvent	temp (°C)	reaction time (h)	prod **4a** yield (%)
1	toluene	rt	24	15
2	toluene	40	24	26
3	toluene	110	3	60
4	THF	66	3	48
5	MeCN	82	3	56

some polymeric material. Finally, the reaction was repeated under reflux for 3 h, whereupon complete consumption of the starting material occurred, and the spiro derivative **4a** was obtained in 60% yield (Table 1). The reaction proceeded analogously (**4a** in 48% yield), when toluene was replaced by tetrahydrofuran (THF), but also in the more polar solvent acetonitrile (**4a** in 56% yield).

After the reaction conditions were optimized, the generality of the reaction was investigated, and the results summarized in Table 2 show that the reaction has a broad applicability. As expected, low yields of **4** were obtained with the less reactive methyl propiolate zwitterionic intermediate (entries 13 and 14).[19]

Concerning the reactions with methyl propiolate the zwitterionic intermediate **6** is formed by attack of the isonitrile moiety to the unsubstituted acetylenic carbon being the more electrophilic terminal carbon, as predicted by the DFT calculation of charge densities (Figure 1) and according to previous experimental results,[19] thus leading to the isolated spiro derivatives **4m** and **4n** in lower yields.

Table 2. Zwitterionic Additions of Acetylenic Esters, Isonitriles, and 3-Cyanochromones

entry	R^1	R^2	R^3	R^4	E	R^5	prod **4**	yield (%)
1	H	H	H	Me	COOMe	*t*-Bu	**4a**	60
2	Me	H	H	Me	COOMe	*t*-Bu	**4b**	61
3	Cl	H	H	Me	COOMe	*t*-Bu	**4c**	54
4	Me	Me	H	Me	COOMe	*t*-Bu	**4d**	55
5	Cl	H	Cl	Me	COOMe	*t*-Bu	**4e**	52
6	H	H	H	Et	COOEt	*t*-Bu	**4f**	62
7	Me	H	H	Et	COOEt	*t*-Bu	**4g**	63
8	Cl	H	H	Et	COOEt	*t*-Bu	**4h**	57
9	Cl	H	Cl	Me	COOMe	*c*-Hex	**4i**	58
10	H	H	H	Et	COOEt	*c*-Hex	**4j**	60
11	Me	H	H	Et	COOEt	*c*-Hex	**4k**	64
12	Cl	H	H	Et	COOEt	*c*-Hex	**4l**	56
13	H	H	H	Me	H	*t*-Bu	**4m**	<3
14	H	H	H	Me	H	*c*-Hex	**4n**	19

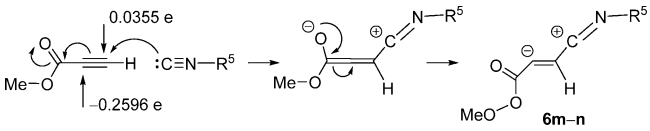


Figure 1. Nucleophilic attack of isonitrile on methyl propiolate; atomic polar tensor (APT) derived charges (with hydrogens summed into heavy atoms) are calculated by DFT (B3LYP/6-31G(d)).

For the formation of the spirobenzofuranocyclopentadienes **4** a plausible mechanism is proposed, as shown in Scheme 2. It is conceivable that the zwitterionic intermediate **6**, initially formed by the 1:1 interaction between the isocyanide and acetylenecarboxylate, attacks preferentially the C-2 chromone carbon leading to intermediate **7**, which upon ring closure gives intermediate **8**. From **8** by 1,5-H shift **5** could be the expected product (path a). However, most probably the reaction follows the unexpected pathway b, whereupon abstraction of the 2-position hydrogen by the isonitrile moiety could lead to the anion intermediate **9**. Subsequently, through the intermediacy of **10**, finally the isolated spiro derivatives **4** can be obtained. To the best of our knowledge no analogous products concerning the chromone moiety have been reported in the literature yet.

To support the above hypothesis density functional theory (DFT) theoretical calculations, using the B3LYP level with the 6-31G(d) basis set as implemented in the Gaussian 03, rev. E.01 package,[20] have been carried out to locate the transition state of this transformation. The formation of new bond between C-2 and C-4 could be initiated in intermediate **9** by an anion attack from the C-2 to carbonyl atom C-4 affording intermediate **10**. The transition state (TS) of this interaction (intermediate **10**) was located using the synchronous transit-guided quasi-newton (STQN) method (QST3 approach),[21] as described analytically in our previous work,[10d] and was calculated to have only one imaginary frequency ($\nu = -309.39$ cm^{-1}). All calculated structures with some critical atom distances are depicted in Figure 2.

The calculated energy profiles for the formation of the anionic intermediates **9a** and **11a** along with that of transition-state intermediate **10a** are shown in Figure 3. Considering the relative free energy of the reaction $\Delta\Delta G^\circ$, which actually shows the relative stability of intermediates **9a** and **11a**, the calculations predict **11a** to be favored over **9a** by 14.37 kcal/mol confirming the experimental formation of only product **4**.

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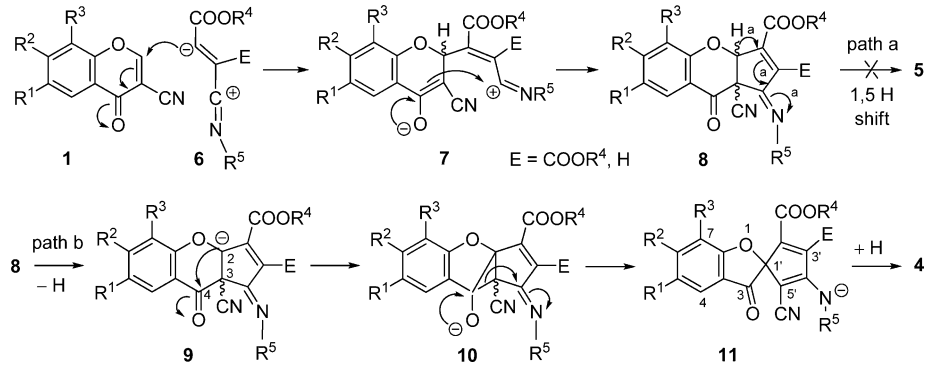
Scheme 2. Mechanistic Rationalization for the Formation of Compounds 4



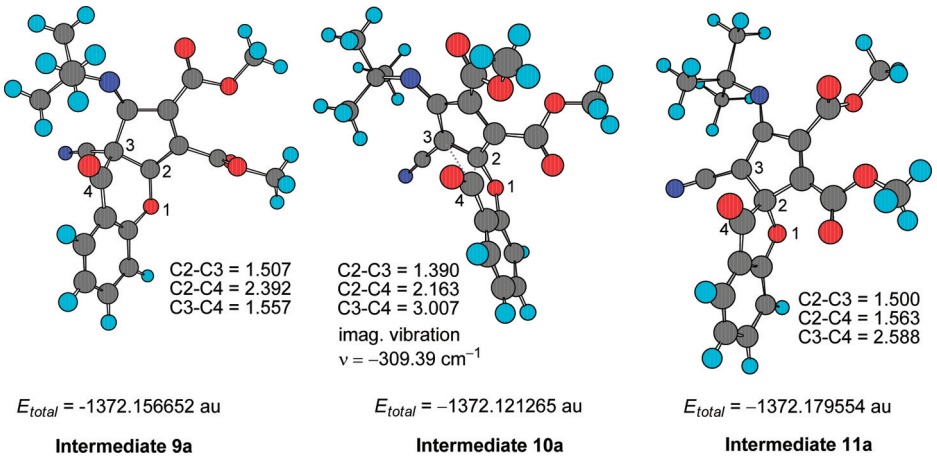


Figure 2. Calculated structures of anion intermediates **9a** (leading to product **5a**), **11a** (leading to product **4a**), and **10a** (transition state between **9a** and **11a**). Atom distances are in angstroms; E_{total} is the sum of electronic and zero-point energy correction (hartrees). The atom numbering is arbitrary, showing the changing of bonds during the transformation.

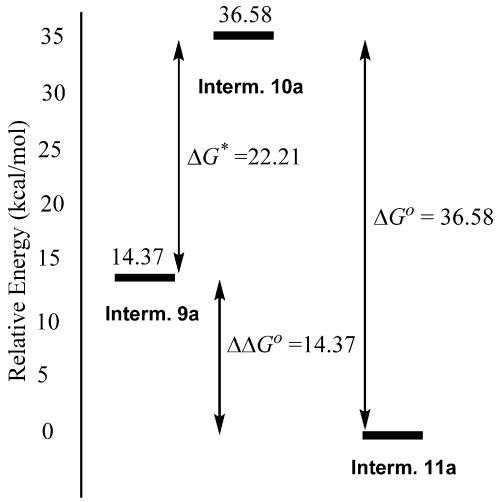


Figure 3. Energy profiles for the formation of the anion intermediates **9a** and **11a**. The energies are expressed in kcal/mol and are given relatively to the most stable intermediate **11a**.

All calculations carried out in vacuo at 298 K. Even when the solvent effect of toluene was evaluated using the polarizable continuum model (PCM),[22] the energy differences remained almost the same.

All spirobenzofuranones **4** exhibited spectral data consistent with their structures [IR, NMR (^{1}H, ^{13}C, COSY, NOESY, HETCOR or HMQC, and COLOC or HMBC), MS, and elemental analysis data]. Thus, the ^{13}C spectrum of **4a** contains a carbonyl signal at δ 193.8, hinting the neighborhood of a sp^3 carbon. In addition, the signal for the quaternary spiro carbon appears at δ 96.8, that of the CN group at δ 117.6, and that of the *tert*-butylamino carbon at δ 53.3. Furthermore, the NH proton at δ 7.17 is of high diagnostic value since it shows intense COLOC correlations with the quaternary carbons at δ 71.8 (C-5′) and at δ 134.5 (C-3′) indicating an almost coplanarity of NH group with the cyclopentadiene ring and revealing a loose hydrogen bond with the 3′-carbonyl oxygen. To the contrary, in **4n** the NH proton resonates at δ 5.30 due to the absence of the 3′-COOMe group.

Moreover, the chemical shift of C-7a for all derivatives is very characteristic, observed downfield at δ ~170 compared to the usual value of δ ~155 for the chromone derivatives.[10] In the ^{1}H NMR of the ethyl derivatives, due to the restricted rotation of the ethyl group, the expected quartet has been changed to a system of doublet of quartets for each combination of conformers, their intensities depending on their molar ratios, and are described as multiplets centered on a particular chemical shift region (~4.0–4.2 ppm).

In Figure 4, the COLOC correlations between protons and carbons via $^2J_{C-H}$ and $^3J_{C-H}$ in compounds **4a** and **4n** are depicted. Some NOESY correlations in **4n** are also indicated. The NOESY correlations in **4n** between the NH proton and the position 3′-proton reveal their proximity and the orientation of the NH proton.

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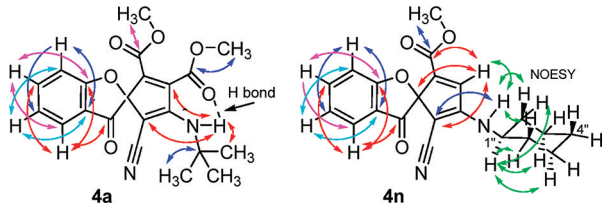

Figure 4. Diagnostic COLOC correlations between protons and carbons (via $^{2}J_{C-H}$ and $^{3}J_{C-H}$) as well as some NOESY correlations in **4a** and in **4n**.

In addition, the structure of compound **4e** was unequivocally confirmed by the use of single-crystal X-ray diffraction analysis (Figure 5).[23]

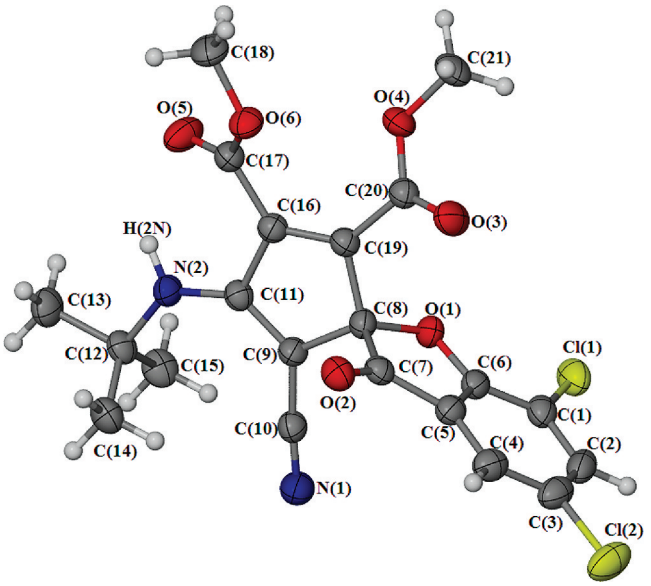

Figure 5. ORTEP diagram of the molecular structure of spirocyclic benzofuranone **4e** as determined by single-crystal XRD (atoms ellipsoid probability 50%).

■ CONCLUSIONS

The new reaction described herein shows a new potential concerning the chromone chemistry leading to the one-pot synthesis of functionalized spirobenzofuranones. The facile and convenient reaction conditions, the cheap reagents, and the absence of expensive transition metal catalysts when compared to existing procedures make this reaction the method of choice in the preparation of substituted spirobenzofuranones as concerns both the economic and the environmental cost. In addition, it constitutes an example of the multidisciplinary way the chromones react, and gives an answer to the question why this moiety appears in so many important biological systems and procedures used in nature. Theoretical DFT calculations, which have been carried out on chromone moieties, support the experimental results.

■ EXPERIMENTAL SECTION

General Methods. Column chromatography was carried out using silica gel, and TLC was performed using precoated silica gel glass plates 0.25 mm containing fluorescent indicator UV_{254} using a 3:1 mixture of petroleum ether−ethyl acetate. Petroleum ether refers to the fraction boiling between 60 and 80 °C. NMR spectra were recorded at room temperature at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively, using $CDCl_3$ as solvent. Chemical shifts are expressed in δ values (ppm) relative to TMS as internal standard for ^{1}H and relative to TMS (0.00 ppm) or to $CDCl_3$ (77.05 ppm) for ^{13}C NMR spectra. Coupling constants ^{n}J are reported in hertz. IR spectra were recorded on a FTIR spectrometer in the form of KBr disks, except in the case of **4n**, and are reported in wave numbers (cm^{-1}). Mass spectra were obtained with the LC-ESI method at 1.65 eV ionization potential and are reported as *m*/*z* (relative intensity to the base peak). Structural assignments of the derived compounds were established by analysis of their IR, MS, and NMR spectra [^{1}H, ^{13}C, COSY, NOESY, HETCOR (or HMQC), and COLOC (or HMBC)] using the standard commercial pulse programs (cosy-45, noesyph-90, D8 = 0.6 s, hmqcqf, hmbclpndqf) and confirmed with XRD analysis.

General Experimental Procedure. *Reaction of 3-Cyanochromones with Dimethyl Acetylenedicarboxylate and tert-Butyl Isocyanide.* To a stirred solution of 3-cyanochromone **1** (1.0 mmol) and dimethyl acetylenedicarboxylate (0.170 g, 1.2 mmol) in toluene (20 mL) was added *tert*-butyl isocyanide (0.1 g, 1.2 mmol) via a syringe, and the reaction mixture was stirred at reflux (110 °C) until chromone **1** was consumed completely (followed by TLC, approximately 3 h). On completion of the reaction, the solvent was removed and the residue was subjected to chromatography on silica gel using petroleum ether/AcOEt (7:1) as eluent, slowly increasing the polarity up to 4:1 to give products **4**.

*Dimethyl 4′-(tert-butylamino)-5′-cyano-3-oxo-3H-spiro[1-benzofuran-2,1′-cyclopenta[2′,4′]diene]-2′,3′-dicarboxylate (**4a**):* orange solid; 0.024 g, yield 60%; mp 183−185 °C (ethanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9 H, $C(CH_3)_3$), 3.59 (s, 3 H, 2′-OCH_3), 3.86 (s, 3 H, 3′-OCH_3), 7.13 (ddd, *J* = 7.7, 7.2, 0.7 Hz, 5-H), 7.17 (br s, 1 H, NH), 7.19 (dd, *J* = 8.4, 0.7 Hz, 1 H, 7-H), 7.65 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1 H, 6-H), 7.75 (dd, *J* = 7.7, 1.4 Hz, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8 ($C(CH_3)_3$), 52.7 (2′-OCH_3), 53.15 (3′-OCH_3), 53.29 ($C(CH_3)_3$), 71.8 (C-5′), 96.8 (C-2), 113.7 (C-7), 117.6 (C≡N), 121.4 (C-3a), 122.5 (C-5), 125.6 (C-4), 134.5 (C-3′), 138.7 (C-6), 145.0 (C-2′), 152.3 (C-4′), 161.1 (2′-C═O), 162.9 (3′-C═O), 171.8 (C-7a), 193.8 (C-3); IR (KBr) ν_{max} 3387, 2184, 1728, 1710 cm^{-1}; LC-MS (ESI, 1.65 eV) *m*/*z* 419 [100, $(M + Na)^+$], 397 [40, $(M + H)^+$]. Anal. Calcd for $C_{21}H_{20}N_2O_6$ (396.39): C, 63.63; H, 5.09; N, 7.07. Found: C, 63.46; H, 5.17; N 7.02.

*Dimethyl 4′-(tert-butylamino)-5′-cyano-5-methyl-3-oxo-3H-spiro[1-benzofuran-2,1′-cyclopenta[2′,4′]diene]-2′,3′-dicarboxylate (**4b**):* orange solid; yield 61%; mp 175−177 °C (CH_2Cl_2−pet ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9 H, $C(CH_3)_3$), 2.37 (s, 3 H, 5-CH_3), 3.62 (s, 3 H, 2′-OCH_3), 3.87 (s, 3 H, 3′-OCH_3), 7.09 (d, *J* = 8.5 Hz, 7-H), 7.22 (br s, 1 H, NH), 7.47 (dd, *J* = 8.5, 1.7 Hz, 1 H, 6-H), 7.53 (d, *J* = 1.7 Hz, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (5-CH_3), 29.8 ($C(CH_3)_3$), 52.8 (2′-OCH_3), 53.19 (3′-OCH_3)*, 53.23 ($C(CH_3)_3$)*, 71.7 (C-5′), 97.1 (C-2), 113.3 (C-7), 117.0 (C≡N), 121.2 (C-3a), 125.0 (C-4), 132.3 (C-5), 134.1 (C-3′), 140.1 (C-6), 145.2 (C-2′), 152.3 (C-4′), 161.2 (2′-C═O), 162.9 (3′-C═O), 170.3 (C-7a), 193.9 (C-3); IR (KBr) ν_{max} 3354, 2186, 1727, 1712 cm^{-1}; LC-MS (ESI, 1.65 eV) *m*/*z* 433 [100, $(M + Na)^+$], 411 [20, $(M + H)^+$]. Anal. Calcd for $C_{22}H_{22}N_2O_6$ (410.42): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.49; H, 5.31; N 6.91. (*The assignments may be interchanged.)

*Dimethyl 4′-(tert-butylamino)-5-chloro-5′-cyano-3-oxo-3H-spiro[1-benzofuran-2,1′-cyclopenta[2′,4′]diene]-2′,3′-dicarboxylate (**4c**):* orange solid; yield 54%; mp 176−178 °C (ethanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9 H, $C(CH_3)_3$), 3.64 (s, 3 H, 2′-OCH_3), 3.88 (s, 3 H, 3′-OCH_3), 7.16 (d, *J* = 8.8 Hz, 7-H), 7.19 (br s, 1 H, NH), 7.60 (dd, *J* = 8.8, 2.0 Hz, 1 H, 6-H), 7.71 (d, *J* = 2.0 Hz, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7 ($C(CH_3)_3$), 52.9 (2′-OCH_3), 53.3 (3′-OCH_3)*, 53.4 ($C(CH_3)_3$)*, 71.2 (C-5′), 97.4 (C-2), 115.0 (C-7), 117.5 (C≡N), 122.4 (C-3a), 124.8 (C-4), 128.2 (C-5), 134.9 (C-3′), 138.6 (C-6), 144.1 (C-2′), 152.3 (C-4′), 160.9 (2′-C═O), 162.8 (3′-C═O), 170.0 (C-7a), 192.9 (C-3); IR (KBr) ν_{max} 3375, 2190, 1736, 1721 cm^{-1}; LC-MS (ESI, 1.65 eV) *m*/*z* 469/471 [50, $(M + K)^+$], 453/455 [100, $(M + Na)^+$]. Anal. Calcd for

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$C_{21}H_{19}ClN_2O_6$ (430.84): C, 58.54; H, 4.45; N, 6.50. Found: C, 58.45; H, 4.51; N 6.38. (*The assignments may be interchanged.)

Dimethyl 4′-(tert-butylamino)-5′-cyano-5,6-dimethyl-3-oxo-3H-spiro[1-benzofuran-2,1′-cyclopenta[2′,4′]diene]-2′,3′-dicarboxylate (**4d**): orange solid; yield 55%; mp 176−178 °C (CH_2Cl_2−pet ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9 H, $C(CH_3)_3$), 2.26 (s, 3 H, 6-CH_3), 2.35 (s, 3 H, 5-CH_3), 3.63 (s, 3 H, 2′-OCH_3), 3.86 (s, 3 H, 3′-OCH_3), 6.99 (s, 1 H, 7-H), 7.22 (br s, 1 H, NH), 7.49 (s, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4 (6-CH_3), 21.6 (5-CH_3), 29.8 ($C(CH_3)_3$), 52.8 (2′-OCH_3), 53.2 (3′-OCH_3, $C(CH_3)_3$), 71.8 (C-5′), 96.9 (C-2), 114.1 (C-7), 117.8 (C≡N), 119.0 (C-3a), 125.2 (C-4), 131.6 (C-5), 133.9 (C-3′), 145.4 (C-2′), 150.2 (C-6), 152.1 (C-4′), 161.3 (2′-C═O), 163.0 (3′-C═O), 170.9 (C-7a), 193.2 (C-3); IR (KBr) ν_{max} 3386, 2182, 1725, 1715 cm^{-1}; LC-MS (ESI, 1.65 eV) m/z 425 [100, $(M + H)^+$]. Anal. Calcd for $C_{23}H_{24}N_2O_6$ (424.45): C, 65.08; H, 5.70; N, 6.60. Found: C, 64.93; H, 5.59; N 6.55.

Diethyl 4′-(tert-butylamino)-5′-cyano-5,7-dichloro-3-oxo-3H-spiro[1-benzofuran-2,1′-cyclopenta[2′,4′]diene]-2′,3′-dicarboxylate (**4e**): orange solid; yield 52%; mp 180−182 °C (ethanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9 H, $C(CH_3)_3$), 3.67 (s, 3 H, 2′-OCH_3), 3.89 (s, 3 H, 3′-OCH_3), 7.12 (br s, 1 H, NH), 7.63 (d, J = 2.0 Hz, 1 H, 6-H), 7.66 (d, J = 2.0 Hz, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7 ($C(CH_3)_3$), 53.0 (2′-OCH_3), 53.4 (3′-OCH_3), 53.5 ($C(CH_3)_3$), 71.0 (C-5′), 97.9 (C-2), 117.2 (C≡N), 119.9 (C-7), 123.2 (C-4), 123.6 (C-3a), 128.4 (C-5), 135.9 (C-5), 137.8 (C-6), 143.0 (C-2′), 152.4 (C-4′), 160.6 (2′-C═O), 162.6 (3′-C═O), 165.7 (C-7a), 192.2 (C-3); IR (KBr) ν_{max} 3341, 2191, 1748, 1712 cm^{-1}; LC-MS (ESI, 1.65 eV) m/z 487/489/491 [100, $(M + Na)^+$]. Anal. Calcd for $C_{21}H_{18}Cl_2N_2O_6$ (465.28): C, 54.21; H, 3.90; N, 6.02. Found: C, 54.14; H, 4.01; N 5.91.

Diethyl 4′-(tert-butylamino)-5′-cyano-3-oxo-3H-spiro[1-benzofuran-2,1′-cyclopenta[2′,4′]diene]-2′,3′-dicarboxylate (**4f**): orange solid; yield 62%; mp 142−144 °C (CH_2Cl_2−pet ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.2, 3 H, CH_3), 1.30 (t, J = 7.1, 3 H, CH_3), 1.51 (s, 9 H, $C(CH_3)_3$), 4.03 (m, 2 H, OCH_2), 4.34 (m, 2 H, OCH_2), 7.13 (dd, J = 7.2, 7.2 Hz, 5-H), 7.20 (d, J = 8.3 Hz, 1 H, 7-H), 7.31 (br s, 1 H, NH), 7.66 (ddd, J = 8.3, 7.2 Hz, 1 H, 6-H), 7.74 (dd, J = 7.2, 1.0 Hz, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2 (CH_3), 13.5 (CH_3), 29.6 ($C(CH_3)_3$), 53.0 ($C(CH_3)_3$), 61.8 (OCH_2), 62.6 (OCH_2), 70.8 (C-5′), 96.6 (C-2), 113.5 (C-7), 117.6 (C≡N), 121.3 (C-3a), 122.3 (C-5), 125.2 (C-4), 134.2 (C-3′), 138.6 (C-6), 145.1 (C-2′), 152.5 (C-4′), 160.2 (2′-C═O), 162.2 (3′-C═O), 171.7 (C-7a), 193.9 (C-3); IR (KBr) ν_{max} 3382, 2184, 1737, 1723 cm^{-1}; LC-MS (ESI, 1.65 eV) m/z 447 [100, $(M + Na)^+$], 425 [30, $(M + H)^+$]. Anal. Calcd for $C_{23}H_{24}N_2O_6$ (424.45): C, 65.08; H, 5.70; N, 6.60. Found: C, 65.16; H, 5.56; N, 6.48.

Diethyl 4′-(tert-butylamino)-5′-cyano-5-methyl-3-oxo-3H-spiro-[1-benzofuran-2,1′-cyclopenta[2′,4′]diene]-2′,3′-dicarboxylate (**4g**): yellow solid; yield 63%; mp 102−104 °C (CH_2Cl_2−pet ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.1 Hz, 3 H, CH_3), 1.31 (t, J = 7.1 Hz, 3 H, CH_3), 1.51 (s, 9 H, $C(CH_3)_3$), 2.36 (s, 3 H, 5-CH_3), 4.05 (m, 2 H, OCH_2), 4.32 (m, 2 H, OCH_2), 7.09 (d, J = 8.4 Hz, 7-H), 7.30 (br s, 1 H, NH), 7.47 (dd, J = 8.4, 1.8 Hz, 1 H, 6-H), 7.52 (d, J = 1.8 Hz, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5 (CH_3), 13.6 (CH_3), 20.6 (5-CH_3), 29.8 ($C(CH_3)_3$), 53.2 ($C(CH_3)_3$), 61.9 (OCH_2), 62.7 (OCH_2), 71.4 (C-5′), 97.1 (C-2), 113.3 (C-7), 117.8 (C≡N), 121.4 (C-3a), 124.9 (C-4), 132.2 (C-5), 133.9 (C-3′), 139.9 (C-6), 145.6 (C-2′), 152.6 (C-4′), 160.6 (2′-C═O), 162.5 (3′-C═O), 170.3 (C-7a), 194.0 (C-3); IR (KBr) ν_{max} 3382, 2185, 1735, 1720 cm^{-1}; LC-MS (ESI, 1.65 eV) m/z 461 [100, $(M + Na)^+$], 439 [30, $(M + H)^+$]. Anal. Calcd for $C_{24}H_{26}N_2O_6$ (438.47): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.62; H, 5.91; N 6.50.

Diethyl 4′-(tert-butylamino)-5-chloro-5′-cyano-3-oxo-3H-spiro-[1-benzofuran-2,1′-cyclopenta[2′,4′]diene]-2′,3′-dicarboxylate (**4h**): yellow solid; yield 57%; mp 144−146 °C (ethanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.1 Hz, 3 H, CH_3), 1.31 (t, J = 7.1 Hz, 3 H, CH_3), 1.51 (s, 9 H, $C(CH_3)_3$), 4.07 (m, 2 H, OCH_2), 4.33 (m, 2 H, OCH_2), 7.16 (d, J = 8.8 Hz, 7-H), 7.29 (br s, 1 H, NH), 7.61 (dd, J = 8.8, 2.2 Hz, 1 H, 6-H), 7.71 (d, J = 2.2 Hz, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5 (CH_3), 13.6 (CH_3), 29.7 ($C(CH_3)_3$), 53.3 ($C(CH_3)_3$), 62.1 (OCH_2), 62.8 (OCH_2), 70.7 (C-5′), 97.5 (C-2), 114.9 (C-7), 117.6 (C≡N), 122.6 (C-3a), 124.7 (C-4), 128.0 (C-5), 134.7 (C-3′), 138.5 (C-6), 144.4 (C-2′), 152.6 (C-4′), 160.2 (2′-C═O), 162.3 (3′-C═O), 170.0 (C-7a), 193.1 (C-3); IR (KBr) ν_{max} 3382, 2184, 1737 cm^{-1}; LC-MS (ESI, 1.65 eV) m/z 459/461 [100, $(M + H)^+$]. Anal. Calcd for $C_{23}H_{23}ClN_2O_6$ (458.89): C, 60.20; H, 5.05; N, 6.10. Found: C, 60.40; H, 5.11; N 6.00.

Dimethyl 5′-cyano-4′-(cyclohexylamino)-5,7-dichloro-3-oxo-3H-spiro[1-benzofuran-2,1′-cyclopenta[2′,4′]diene]-2′,3′-dicarboxylate (**4i**): orange solid; yield 58%; mp 162−164 °C (ethanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20−1.52 (m, 5 H, 2″,3″,4″,5″,6″-H_{ax}), 1.56−1.80 (m, 3 H, 3″,4″,5″-H_{eq}), 2.01−2.19 (m, 2 H, 2″,6″-H_{eq}), 3.80−3.95 (m, 1 H, 1″-H_{eq}), 3.66 (s, 3 H, OCH_3), 3.85−3.94 (m, 1 H, 3″-H), 3.89 (s, 3 H, OCH_3), 6.71(d, J = 7.6 Hz, 1 H, NH), 7.63 (d, J = 2.1 Hz, 1 H, 6-H), 7.66 (d, J = 2.1 Hz, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8 and 23.9 (C-3″,C-5″), 25.2 (C-4″), 33.8 and 33.9 (C-2″,C-6″), 52.7 (C-1″), 53.0 (2-OCH_3), 53.3 (OCH_3), 70.1 (C-5′), 97.2 (C≡N), 115.5 (C-2), 120.0 (C-7), 123.2 (C-4), 123.6 (C-3a), 128.4 (C-5), 134.9 (C-3′), 137.8 (C-6), 143.6 (C-2′), 154.5 (C-4′), 160.5 (2′-C═O), 162.3 (3′-C═O), 165.7 (C-7a), 192.3 (C-3); IR (KBr) ν_{max} 3385, 2188, 1740, 1722 cm^{-1}; LC-MS (ESI, 1.65 eV) m/z 513/515/517 [100, $(M + Na)^+$]. Anal. Calcd for $C_{23}H_{20}Cl_2N_2O_6$ (491.32): C, 56.23; H, 4.10; N, 5.70. Found: C, 56.10; H, 4.01; N 5.61.

Diethyl 5′-cyano-4′-(cyclohexylamino)-3-oxo-3H-spiro[1-benzofuran-2,1′-cyclopenta[2′,4′]diene]-2′,3′-dicarboxylate (**4j**): yellow crystals; yield 60%; mp 129−131 °C (CH_2Cl_2−pet ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.1, 3 H, CH_3), 1.31 (t, J = 7.1, 3 H, CH_3), 1.20−1.53 (m, 5 H, 2″,3″,4″,5″,6″-H_{ax}), 1.57−1.80 (m, 3 H, 3″,4″,5″-H_{eq}), 2.03−2.18 (m, 2 H, 2″,6″-H_{eq}), 3.82−3.94 (m, 1 H, 1″-H_{eq}), 4.03 (m, 2 H, OCH_2), 4.34 (m, 2 H, OCH_2), 6.87 (d, J = 8.2 Hz, 1 H, NH), 7.14 (ddd, J = 7.6, 7.3, 0.7 Hz, 5-H), 7.19 (dd, J = 8.4, 0.7 Hz, 1 H, 7-H), 7.66 (ddd, J = 8.4, 7.3, 1.5 Hz, 1 H, 6-H), 7.75 (dd, J = 7.6, 1.5 Hz, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3 (CH_3), 13.7 (CH_3), 24.8 and 24.9 (C-3″,C-5″), 25.3 (C-4″), 32.8 and 33.9 (C-2″,C-6″), 52.4 (C-1″), 61.9 (OCH_2), 62.6 (OCH_2), 70.2 (C-5′), 96.1 (C≡N), 113.7 (C-7), 116.1 (C-2), 121.5 (C-3a), 122.4 (C-5), 125.5 (C-4), 133.4 (C-3′), 138.7 (C-6), 145.7 (C-2′), 154.7 (C-4′), 160.3 (C═O), 162.1 (C═O), 171.8 (C-7a), 194.1 (C═O); IR (KBr) ν_{max} 3311, 2187, 1746, 1724 cm^{-1}; LC-MS (ESI, 1.65 eV) m/z 451 [100, $(M + H)^+$]. Anal. Calcd for $C_{25}H_{26}N_2O_6$ (450.48): C, 66.65; H, 5.82; N, 6.22. Found: C, 66.66; H, 5.76; N 6.38.

Diethyl 5′-cyano-4′-(cyclohexylamino)-5-methyl-3-oxo-3H-spiro-[1-benzofuran-2,1′-cyclopenta[2′,4′]diene]-2′,3′-dicarboxylate (**4k**): yellow crystals; yield 64%; mp 102−104 °C (CH_2Cl_2−pet ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.1, 3 H, CH_3), 1.31 (t, J = 7.1, 3 H, CH_3), 1.24−1.55 (m, 5 H, 2″,3″,4″,5″,6″-H_{ax}), 1.55−1.77 (m, 3 H, 3″,4″,5″-H_{eq}), 2.03−2.17 (m, 2 H, 2″,6″-H_{eq}), 2.37 (s, 3 H, CH_3), 3.82−3.92 (m, 1 H, 1″-H_{eq}), 4.04 (m, 2 H, OCH_2), 4.31 (m, 2 H, OCH_2), 6.87 (d, J = 8.2 Hz, 1 H, NH), 7.08 (d, J = 8.5 Hz, 1 H, 7-H), 7.47 (ddd, J = 8.5, 1.8 Hz, 1 H, 6-H), 7.53 (d, J = 1.8 Hz, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5 (CH_3), 13.7 (CH_3), 20.6 (5-CH_3), 23.8 and 23.9 (C-3″,C-5″), 25.4 (C-4″), 32.8 and 33.0 (C-2″,C-6″), 52.4 (C-1″), 61.9 (OCH_2), 62.6 (OCH_2), 70.6 (C-5′), 96.5 (C-2), 113.3 (C-7), 116.1 (C≡N), 121.5 (C-3a), 124.9 (C-4), 132.2 (C-5), 133.1 (C-3′), 139.9 (C-6), 146.0 (C-2′), 154.6 (C-4′), 160.5 (C═O), 162.1 (C═O), 170.4 (C-7a), 194.0 (C-3); IR (KBr) ν_{max} 3296, 2187, 1738, 1723, 1695 cm^{-1}; LC-MS (ESI, 1.65 eV) m/z 487 [100, $(M + Na)^+$], 465 [60, $(M + H)^+$]. Anal. Calcd for $C_{26}H_{28}N_2O_6$ (464.51): C, 67.23; H, 6.08; N, 6.03. Found: C, 67.36; H, 5.99; N 6.08.

Diethyl 5-chloro-5′-cyano-4′-(cyclohexylamino)-3-oxo-3H-spiro-[1-benzofuran-2,1′-cyclopenta[2′,4′]diene]-2′,3′-dicarboxylate (**4l**): orange crystals; yield 56%; mp 141−143 °C (ethanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.0, 3 H, CH_3), 1.32 (t, J = 7.3, 3 H, CH_3), 1.20−1.50 (m, 5 H, 2″,3″,4″,5″,6″-H_{ax}), 1.57−1.81 (m, 3 H, 3″,4″,5″-H_{eq}), 2.02−2.18 (m, 2 H, 2″,6″-H_{eq}), 3.80−3.93 (m, 1 H, 1″-H_{eq}), 4.07 (m, 2 H, OCH_2), 4.33 (m, 2 H, OCH_2), 6.86 (d, J = 8.3 Hz, 1 H, NH), 7.16 (d, J = 8.8 Hz, 1 H, 7-H), 7.61 (dd, J = 8.8, 2.3 Hz, 1 H, 6-H), 7.72 (d, J = 2.3 Hz, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5 (CH_3), 13.7 (CH_3), 23.8 and 23.9 (C-3″,C-5″), 25.2 (C-4″), 32.7 and 32.8 (C-2″,C-6″), 52.5 (C-1″), 62.1 (OCH_2), 62.7 (OCH_2), 69.8 (C-5′), 96.8 (C-2), 115.0 (C-7), 115.9 (C≡N), 122.6 (C-3a),

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124.7 (C-4), 128.0 (C-5), 133.8 (C-3′), 138.5 (C-6), 144.8 (C-2′), 154.6 (C-4′), 160.1 (2′-C═O), 161.9 (3′-C═O), 170.0 (C-7a), 193.1 (C-3); IR (KBr) ν_{max} 3391, 2188, 1751, 1728, 1712 cm^{-1}; LC-MS (ESI, 1.65 eV) m/z (%) 485/487 [100, $(M + H)^+$]. Anal. Calcd for $C_{25}H_{25}ClN_2O_6$ (484.93): C, 61.92; H, 5.20; N, 5.78. Found: C, 62.06; H, 5.12; N 5.88.

*Methyl 5′-cyano-4′-(cyclohexylamino)-3-oxo-3H-spiro[1-benzofuran-2,1′-cyclopenta[2′,4′]diene]-2′-carboxylate (**4n**):* oil; 0.069 g; yield 19%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18−1.35 (m, 2 H, 2″,6″-H_{ax}), 1.35−1.52 (m, 2 H, 3″,5″-H_{ax}), 1.55−1.70 (m, 2 H, 4″-H), 1.70−1.83 (m, 2 H, 3″,5″-H_{eq}), 2.03−2.17 (m, 2 H, 2″,6″-H_{eq}), 3.59 (s, 3 H, OCH_3), 3.67−3.83 (m, 1 H, 1″-H_{ax}), 5.27 (br d, J = 7.8 Hz, 1 H, NH), 7.04 (br s, 1 H, 3′-H), 7.12 (ddd, J = 7.7, 7.3, 0.7 Hz, 5-H), 7.18 (ddd, J = 8.4, 0.7 Hz, 0.6 Hz, 1 H, 7-H), 7.65 (ddd, J = 8.4, 7.3, 1.4 Hz, 1 H, 6-H), 7.73 (dd, J = 7.7, 1.4, 0.6 Hz, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2 (C-3″,5″), 25.2 (C-4″), 33.5 (C-2″,6″), 52.2 (2′-OCH_3), 53.4 (C-1″), 73.8 (C-5′), 95.9 (C-2), 113.6 (C-7), 115.9 (C≡N), 121.5 (C-3a), 122.1 (C-5), 125.3 (C-4), 138.6 (C-6), 140.5 (C-2′), 140.6 (C-3′), 157.0 (C-4′), 160.7 (2′-C═O), 172.2 (C-7a), 195.7 (C-3); IR (neat) ν_{max} 3385, 2181, 1730 cm^{-1}; LC-MS (ESI, 1.65 eV) m/z 387 [100, $(M + Na)^+$]. Anal. Calcd for $C_{21}H_{20}N_2O_4$ (364.40): C, 69.22; H, 5.53; N, 7.69. Found: C, 69.43; H, 5.47; N, 7.53.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra for all novel compounds. Optimized geometries (in Cartesian coordinates) for anion intermediates **9a**, **10a**, and **11a**. Crystallographic data, bond lengths, bond angles, and structure refinement for compound **4e**. Crystallographic information for **4e** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Complete crystallographic data for compound **4e** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 824795. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: 0044 1223 336 033, e-mail: deposit@ccdc.cam.ac.uk).