Regioselective Synthesis of Novel Spiropyrrolidines and Spirothiapyrrolizidines Through Multicomponent 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylides

Hai Liu, Guolan Dou, and Daqing Shi*

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou, Jiangsu 215123, P. R. China

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A series of novel spiropyrrolidines and spirothiapyrrolizidines were synthesized via a three-component 1,3-dipolar cycloaddition reaction of isatin or acenaphthenequinone, sarcosine or thiaproline and 4-hydroxy-6-methyl-3-((*E*)-3-phenylacryloyl)-2*H*-pyran-2-ones in refluxing ethanol. Advantages of this method include the availability of starting materials, mild reaction conditions, high yields, and the complete regioselectivity observed.

Introduction

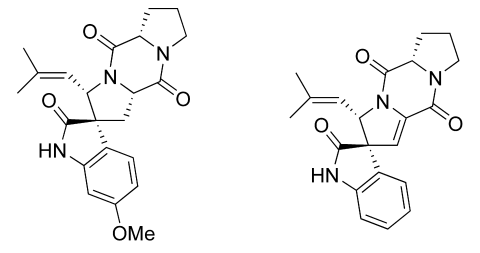
Exploring novel pharmacological agents with minimum number of synthetic steps and less time is a major challenge for chemists.[1] In general, the conventional approach involves the use of multistep reaction sequences which are typically associated with low yields, high cost, and tedious isolation and purification of the resulting products. However, as a significant strategy superior to the conventional one, multicomponent reactions (MCRs) offer a valuable solution for such a situation.[2−7] MCRs constitute a highly effective one-pot procedure that has many advantages, including atom economy[8] and facile synthesis of molecules that have interesting biological properties using readily available starting materials. Multicomponent 1,3-dipolar cycloaddition reactions play a key role in the synthesis of five-membered heterocyclic compounds.[9] 1,3-Dipolar cycloaddition reactions of azomethine ylides with olefinic and acetylenic dipolarophiles represent an important approach for the formation of pyrrolidines and pyrrolizines which are prevalent in a variety of biologically active compounds.[10] In recent years, construction of spiro compounds by 1,3-dipolar cycloaddition reactions of azomethine ylides has been well developed, and the reactions proceed with high regio- and stereoselectivity.[11,12]

The indole core represents an interesting pharmacophore which displays the feature of biological and pharmacological properties.[13] Furthermore, the 3′-spirooxindoles formed by sharing of the 3-carbon atom have been of interest to organic chemists because spirooxindole derivatives are characterized by interesting biological properties.[14−16] For instance, Spirotryprostatin A and B (Figure 1), which have been isolated from the fermentation broth of *Aspergillus fumigatus*, have been identified as novel inhibitors of microtubule assembly.[17] Derivatives of spirooxindole exhibit a range of biological properties, including antimicrobial, antitumoral, antibiotic agents, and inhibitors of human NK-1 receptor.[18]

Many 4-pyrones or compounds containing the 4-pyrone moiety which have been synthesized over the past few decades have biological activities, such as herbicidal, fungicidal, antiallergenic, and anticancer activity.[19] Hagan et al have described the synthesis of pyrone-containing novel anti-AIDS drugs that display superior characteristics over the corresponding nucleoside-containing derivatives.[20] To our knowledge there is no report on the synthesis of spiropyrrolidines and spirothiapyrrolizidines containing a pyrone moiety. As part of our interest in 1,3-dipolar cycloaddition reactions,[21] we report herein the facile synthesis of novel spiropyrrolidine and spirothiapyrrolizidine derivatives having a pyrone moiety via a one-pot, three-component 1,3-dipolar cycloaddition reaction of azomethine ylides.

Results and Discussion

The choice of an appropriate reaction medium is of crucial importance for successful synthesis. Initially, the three-component reaction of isatin **1a**, sarcosine **2** and 4-hydroxy-6-methyl-3-((*E*)-3-*p*-tolylacryloyl)-2*H*-pyran-2-one **3a** as a simple model substrate was investigated to establish the feasibility of the strategy and to optimize the reaction conditions (Scheme 1). Different solvents such as methanol, ethanol, acetonitrile, tetrahydrofuran (THF), 1,4-dioxane, and dichloromethane were explored. The results are summarized in Table 1. As can be seen from Table 1, the best results were obtained by refluxing the reaction mixture in ethanol



Spirotryprostatin A Spirotryproatatin B

Figure 1. Structures of Spirotryprostatin A and B.

* To whom correspondence should be addressed. E-mail: dqshi@suda.edu.cn.

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Scheme 1. Synthesis of Spiropyrrolidines **4a**−**j**

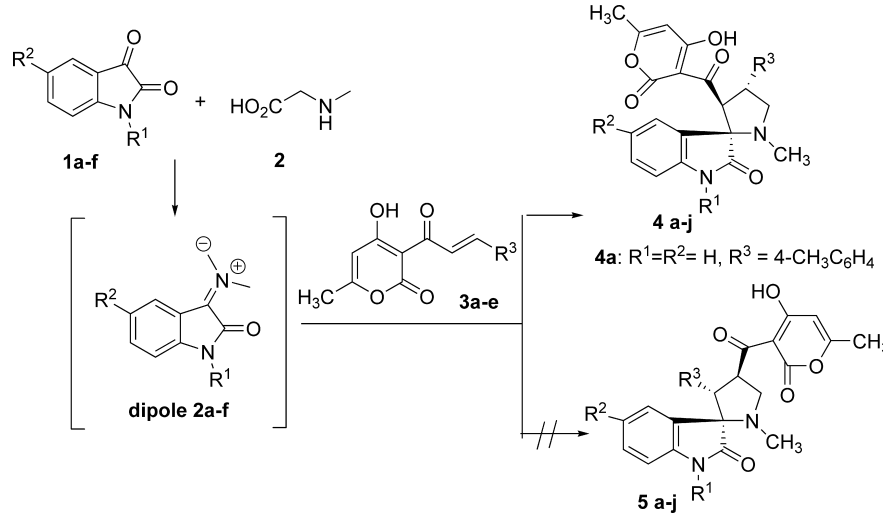


Table 1. Synthetic Results of **4a** under Different Reactions Conditions

entry	solvent	temper./°C	time/h	isolated yield/%
1	ethanol	reflux	1.5	92
2	methanol	reflux	2	84
3	acetonitrile	reflux	6.5	86
4	1,4-dioxane	reflux	12	75
5	THF	reflux	12	38
6	dichloromethane	reflux	12	13

to yield product **4a** as a single regioisomer in high yield (Table 1, Entry 1).

Encouraged by this success, we extended this reaction of isatins **1a**−**f** with sarcosine **2** and 4-hydroxy-6-methyl-3-((*E*)-3-phenylacryloyl)-2*H*-pyran-2-ones **3a**−**e** under optimized conditions. The corresponding spiropyrrolidines **4a**−**j** were synthesized in high yield (87−97%), and the results are summarized in Table 2. It can be seen from the Table 2 that the nature of the substituents in isatins and aryl groups on the 4-hydroxy-6-methyl-3-((*E*)-3-phenylacryloyl)-2*H*-pyran-2-ones had no significant effect on the final yield of the products.

Table 2. Synthetic Results of Spiropyrrolidines **4a**−**j** via Three-Component Reaction

entry	R^1	R^2	R^3	products	isolated yield/%
1	H	H	4-$CH_3C_6H_4$	**4a**	92
2	H	Br	4-$CH_3C_6H_4$	**4b**	92
3	H	Cl	4-$CH_3C_6H_4$	**4c**	87
4	H	F	4-$CH_3C_6H_4$	**4d**	88
5	H	CH_3	4-$CH_3C_6H_4$	**4e**	91
6	CH_3	H	4-$CH_3C_6H_4$	**4f**	97
7	H	H	4-$CH_3OC_6H_4$	**4g**	92
8	H	H	4-$NO_2C_6H_4$	**4h**	95
9	H	H	4-BrC_6H_4	**4i**	94
10	H	H	C_6H_5	**4j**	93

Although the detailed mechanism of the above reaction is not fully clarified, the formation of regioisomer **4a** could be explained as follows: decarboxylative condensation of the isatin **1a** with sarcose **2** gives the azomethine ylide (dipole **2a**) which then undergoes 1,3-dipolar cycloaddition reaction reaction with the dipolarophile (**3a**) regioselectively as shown in Figure 2 (Part A). The regioselectivity in the product formation can be explained by considering the secondary orbital interaction (**SOI**)[22] of the orbital of the carbonyl group

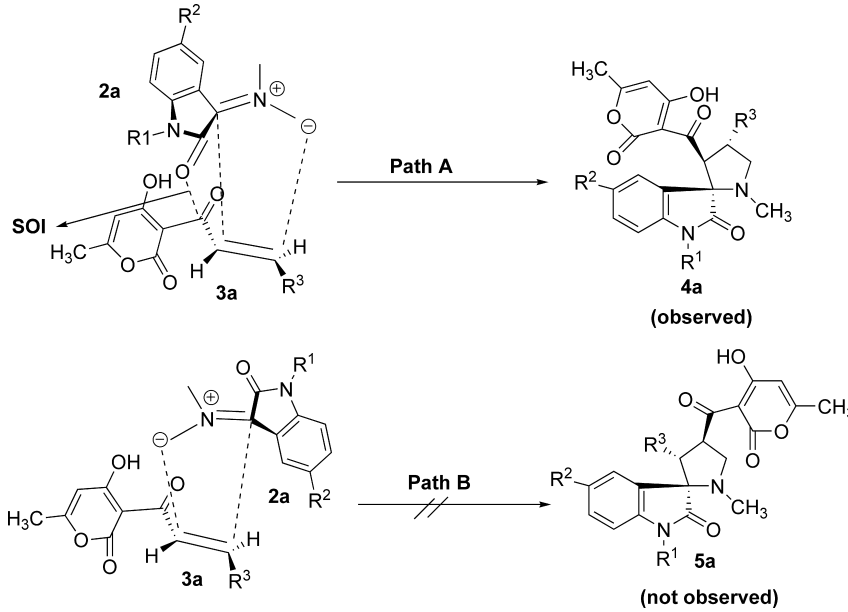


Figure 2. Mode of Approach of Azomethine Ylide **2a**.

Scheme 2. Synthesis of Spirothiapyrrolizidines **7a−i**

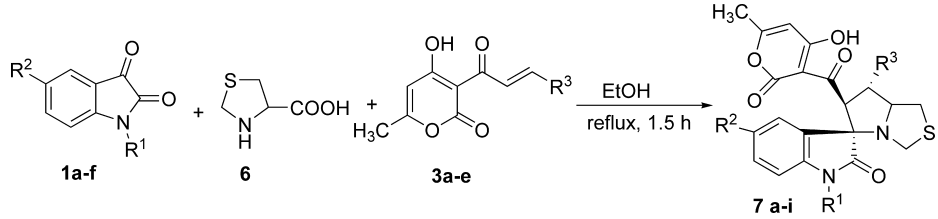


Table 3. Synthetic Results of Spirothiapyrrolizidines **7a−i** via Three-Component Reaction

entry	R^1	R^2	R^3	products	isolated yield/%
1	H	H	4-$CH_3C_6H_4$	**7a**	93
2	H	Br	4-$CH_3C_6H_4$	**7b**	92
3	H	Cl	4-$CH_3C_6H_4$	**7c**	94
4	H	F	4-$CH_3C_6H_4$	**7d**	85
5	H	CH_3	4-$CH_3C_6H_4$	**7e**	90
6	CH_3	H	4-$CH_3C_6H_4$	**7f**	94
7	H	H	4-$CH_3OC_6H_4$	**7g**	93
8	H	H	4-$NO_2C_6H_4$	**7h**	95
9	H	H	4-BrC_6H_4	**7i**	91

Table 4. Synthetic Results of Spiropyrrolidines **9a−d** and Spirothiapyrrolizidines **10a−d** via Three-Component Reactions

entry	R^3	products	isolated yield/%
1	4-$CH_3OC_6H_4$	**9a**	92
2	4-$NO_2C_6H_4$	**9b**	95
3	4-$CH_3C_6H_4$	**9c**	93
4	C_6H_5	**9d**	91
5	4-$CH_3OC_6H_4$	**10a**	92
6	4-$NO_2C_6H_4$	**10b**	96
7	4-$CH_3C_6H_4$	**10c**	93
8	C_6H_5	**10d**	92

of dipolarophile **3** with those of the ylide **2a** as shown in Figure 2. Accordingly, the observed regioisomer **4a** via path **A** is more favorable because of the secondary orbital interaction which is not possible in path **B**.

When the sarcosine **2** was replaced by thiaproline **6**, a series of spirothiapyrrolizidines **7** were obtained under the same reaction conditions (Scheme 2). The results are summarized in Table 3.

To expand the scope of this three-component 1,3-dipolar cycloaddition reaction, the reaction of acenaphthenequinone **8** and 4-hydroxy-6-methyl-3-((*E*)-3-phenylacryloyl)-2*H*-pyran-2-ones **3** with sarcosine **2** or thiaproline **6** was attempted. The corresponding spiropyrrolidines **9** and spirothiapyrrolizidines **10** were obtained in good yields (Scheme 3), and the results are summarized in Table 4.

The structures of final products **4**, **7**, **9**, and **10** were established by IR, ^{1}H NMR, and ^{13}CNMR spectroscopy. The structures of compounds **7b**, **9c**, and **10c** were confirmed by X-ray analysis. The X-ray crystal structure of **7b** is represented in Figures 3.

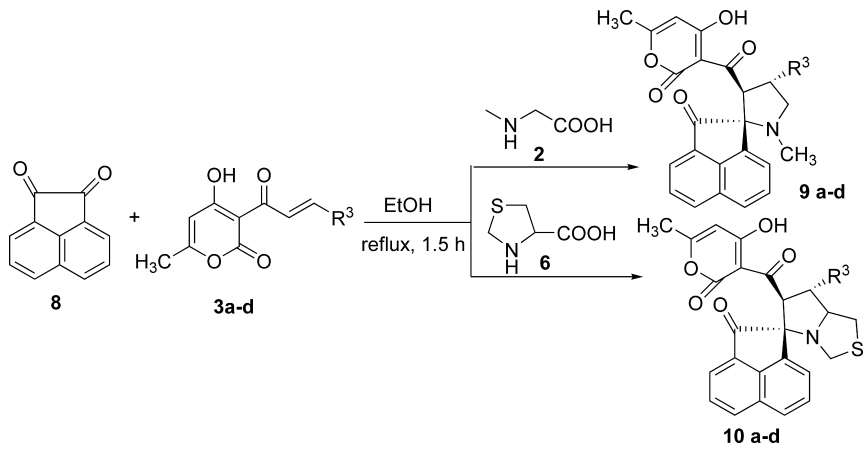
In conclusion, we have developed an efficient and regioselective three-component 1,3-dipolar cycloaddition reaction for the synthesis of spiropyrrolidines and spirothiapyrrolizidines that incorporate in their structures a pyrone moiety. This method has the advantages of good yields, mild reaction conditions, easy workup, readily available starting materials, and high regioselectivity.

Experimental Section

General Information. Melting points were determined in open capillaries and are uncorrected. Infrared spectra were recorded on a Varian F-1000 spectrophotomer as KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Inova-400 MHz or Inova-300 MHz spectrometer as DMSO-d_6 solution. *J* values are in hertz (Hz). Chemical shifts are expressed in δ downfield from internal tetramethylsilane. HRMS were obtained using a TOF-MS or Bruker micrOTOF-Q instrument. X-ray crystallographic analysis was performed with a Siemens P4 or Smart-1000 CCD diffractometer.

General Procedure for the Synthesis of Compound 4 and 7. A dry 50 mL flask was charged with isatins **1** (0.5 mmol), sarcosine **2** or thiaproline **6** (0.5 mmol), 4-hydroxy-6-methyl-3-((*E*)-3-phenylacryloyl)-2*H*-pyran-2-one **3** (0.5 mmol), and ethanol (5 mL). The reaction mixture was stirred at refluxing temperature for 1.5 h. After completion of the reaction, the solvent was removed under vacuum. The solid was recrystallized from ethanol, and then dried to give products **4** or **7**.

Scheme 3. Synthesis of Spiropyrrolidines **9a−d** and Spirothiapyrrolizidines **10a−d**



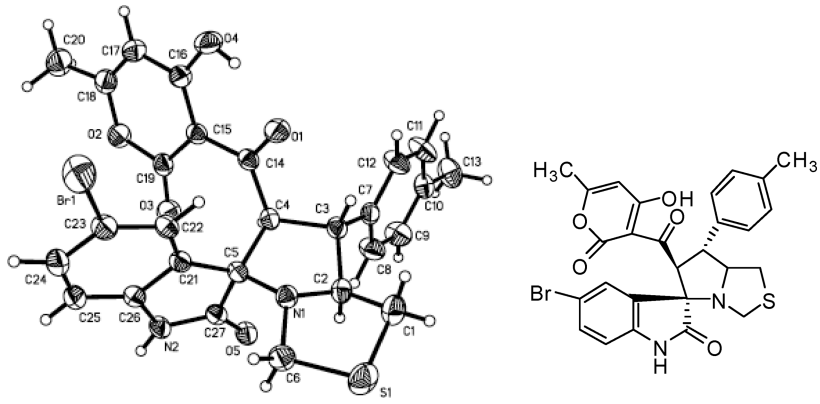


Figure 3. X-ray Structure of **7b**.

Compound 4b. Compound **4b** (240 mg) was obtained in 92% yield, mp 250−251 °C; IR (KBr) 3378, 3161, 3083, 2968, 2851, 2793, 1724, 1641, 1552, 1458, 1313, 1236, 1185, 994, 928, 811 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.00 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.21−3.24 (m, 1H, CH-H), 3.39−3.46 (m, 1H, CH-H), 4.31 (d, J = 7.2 Hz, 1H, CH), 4.71 (d, J = 8.4 Hz, 1H, CH), 6.13 (s, 1H, =CH), 6.66 (d, J = 7.8 Hz, 1H, ArH), 6.86 (s, 1H, ArH), 7.10 (d, J = 6.9 Hz, 2H, ArH), 7.27 (d, J = 6.9 Hz, 3H, ArH), 10.53 (s, 1H, NH), 15.68 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 20.60, 21.27, 34.75, 42.96, 59.86, 63.96, 73.10, 100.31, 101.37, 111.87, 113.43, 128.29, 128.51, 129.65, 129.78, 132.52, 136.47, 138.92, 143.44, 160.74, 171.08, 179.11, 180.09, 203.75; HRMS calculated for $C_{26}H_{24}BrN_2O_5$ [M+H]: 523.0863, found 523.0873.

Compound 7c. Compound **7c** (245 mg) was obtained in 94% yield, mp 232−233 °C; IR (KBr) 3448, 3179, 3032, 2926, 1885, 2821, 1724, 1640, 1552, 1452, 1377, 1311, 1200, 1122, 997, 937, 817, 777 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.08 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.73 (t, J = 8.4 Hz, 1H, CH-H), 2.82−2.87 (m, 1H, CH-H), 3,39 (d, J = 6.9 Hz, 1H, CH-H), 3.45 (d, J = 6.9 Hz, 1H, CH-H), 3.90 (t, J = 9.6 Hz, 1H, CH), 4.18−4.25 (m, 1H, CH), 5.05 (d, J = 9.9 Hz, 1H, CH), 6.08 (s, 1H, =CH), 6.71 (d, J = 8.4 Hz, 1H, ArH), 6.96 (s, 1H, ArH), 7.12 (d, J = 7.8 Hz, 2H, ArH), 7.18 (dd, J_1 = 5.1 Hz, J_2 = 8.4 Hz, 1H, ArH), 7.30 (d, J = 7.8 Hz, 2H, ArH), 10.63 (s, 1H, NH), 15.02 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 20.61, 21.28, 32.85, 47.58, 48.33, 67.10, 70.10, 73.06, 100.32, 101.20, 111.69. 125.77, 126.32, 127.40, 128.48, 129.99, 130.16, 136.93, 137.36, 142.62, 161.75, 170.73, 178.43, 178.99, 201.54; HRMS calculated for $C_{27}H_{23}ClN_2O_5S$ 522.1016, found 522.1012.

General Procedure for the Synthesis of Compound 9 and 10. A dry 50 mL flask was charged with acenaphthenequinone **8** (0.5 mmol), sarcosine **2** or thiaproline **6** (0.5 mmol), 4-hydroxy-6-methyl-3-((*E*)-3-phenylacryloyl)-2*H*-pyran-2-one **3** (0.5 mmol), and ethanol (5 mL). The reaction mixture was stirred at refluxing temperature for 1.5 h. After completion of the reaction, the solvent was removed under vacuum. The solid was recrystallized from ethanol, and then dried to give products **9** or **10**.

Compound 9a. Compound **9a** (228 mg) was obtained in 92% yield, mp 162−164 °C; IR (KBr) 3417, 3053, 2932, 2846, 2788, 1721, 1643, 1555, 1451, 1312, 1244, 1175, 1030, 927, 835, 785 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.89 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 3.40 (d, J = 7.6 Hz, 1H, CH-H), 3.56 (t, J = 9.2 Hz, 1H, CH-H), 3.72 (s, 3H, OCH_3), 4.43−4.49 (m, 1H, CH), 4.83 (d, J = 9.2 Hz, 1H, CH), 5.94 (s, 1H, =CH), 6.92 (d, J = 8.0 Hz, 2H, ArH), 7.28 (d, J = 6.8 Hz, 1H, ArH), 7.38 (d, J = 8.4 Hz, 2H, ArH), 7.57 (t, J = 7.6 Hz, 1H, ArH), 7.79 (t, J = 7.2 Hz, 1H, ArH), 7.87 (t, J = 8.0 Hz, 2H, ArH), 8.18 (d, J = 8.0 Hz, 1H, ArH), 15.70 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 20.36, 34.81, 43.00, 55.72, 60.83, 64.34, 76.75, 100.46, 101.17, 114.75, 121.14, 122.24, 125.83, 128.96, 129.08, 129.51, 130.25, 131.94, 132.17, 133.91, 137.48, 142.31, 158.81, 160.47, 170.60, 179.71, 204.02, 207.93; HRMS calculated for $C_{30}H_{26}NO_6$ [M+H]: 496.1755, found: 496.1746.

Compound 10c. Compound **10c** (243 mg) was obtained in 93% yield, mp 213−215 °C; IR (KBr) 3424, 3056, 2933, 2862, 1725, 1641, 1554, 1455, 1335, 1241, 1173, 1058, 998, 836, 786 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.91 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.87 (s, 1H, CH-H), 3.00 (s, 1H, CH-H), 3.44 (s, 1H, CH-H), 3.53 (s, 1H, CH-H), 4.07 (s, 1H, CH), 4.33 (s, 1H, CH), 5.12 (s, 1H, CH), 5.85 (s, 1H, =CH), 7.18 (s, 2H, ArH), 7.40 (s, 2H, ArH), 7.51 (s, 1H, ArH), 7.60 (s, 1H, ArH), 7.80 (s, 1H, ArH), 7.93 (s, 2H, ArH), 8.20 (s, 1H, ArH), 14.86 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 20.33, 21.29, 33.73, 49.04, 50.73, 66.02, 73.59, 75.54, 100.62, 101.02, 122.21, 123.77, 126.39, 128.53, 128.73, 129.02, 130.08, 130.65, 131.46, 132.26, 134.75, 136.95, 137.54, 141.95, 160.56, 170.11, 178.40, 201.83, 204.02; HRMS calculated for $C_{31}H_{26}NO_5S$ [M+H]: 524.1526, found: 524.1521.

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Supporting Information Available. Experimental procedures and IR, ^1H NMR,^{13}C NMR and MS spectra for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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