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Hetero-Diels–Alder (HDA) Strategy for the Preparation of 6-Aryl- and Heteroaryl-Substituted Piperidin-2-one Scaffolds: Experimental and Theoretical Studies

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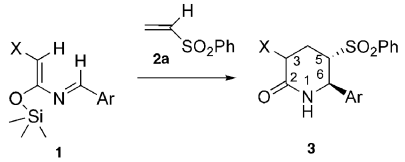
Preparation of piperidine-2-one scaffolds by the hetero-Diels–Alder (HAD) reaction, assisted by microwaves, is described. The versatility of this new approach has been demonstrated by the synthesis of racemic (±)-2-phenylpiperidine. Theoretical calculations have allowed us to clarify the factors that govern ring closure to form four-membered rings, arising from a Staudinger-type electrocyclization, and/or six-membered rings through a classical [4+2] HAD cyclization. This competition may be lowered by increasing the electronic demand of the dienophile, as anticipated by the computational studies.

Introduction

Functionalized 2-azadienes are versatile intermediates for the preparation of five- and six-membered heterocycles.[1–4] In this area, we and other research group[5–9] have been interested in the use of functionalized azadiene system **1** (Scheme 1) for the preparation of heterocyclic compounds, such as β-lactam rings, by a two-step Staudinger reaction,[10–12] as well as tetramic acid scaffolds,[13] perhydrooxazin-2-ones, cyclic intermediates in the synthesis of α-amino β-hydroxy acids,[14,15] β-hydroxycarboxylic acids,[16] and 1,3-aminols, through a hetero-Diels–Alder (HDA) approach.[17–20] Some processes have been performed by taking advantage of microwave-assisted organic synthesis (MAOS) technology.[21–23] More recently, the HDA-approach has been used for the synthesis of conhydrine, which is a poisonous alkaloid present in *Conium maculatum* and characterized by a piperidine scaffold.[24] Herein, we report the natural progress of our studies in this area by extending the preparative utility of this new approach to piperidine-2-one heterocyclic rings substituted in the 6-position by an aromatic or heteroaromatic group.[25–30] The synthetic protocol for the preparation of the starting azadiene **1** was that already published: synthesis of a *N*-(trimethylsilyl)imine[31] and coupling of this intermediate with a suitable acyl chloride in the presence of a base, such as triethylamine.[32] To obtain the target piperidine-2-one scaffold, the azadiene thus prepared was reacted with a dienophilic moiety with two carbon atoms to allow the formation of a six-membered heterocyclic ring (Scheme 1). The intrinsic characteristic flexibility of a sulfonyl group, which may be easily removed, according well-established literature protocols, or elaborated to more complex decorations of the heterocyclic ring, drove our choice towards the vinylsulfone **2a** (Scheme 1), which presents, additionally, the necessary electron-poor nature for a normal electron demand hetero-Diels–Alder (HAD) reaction.



Scheme 1. Reaction of azadienes **1a**–**e** with dienophile **2a**.

Results and Discussion

Reaction of azadiene **1a** with vinylsulfone **2a** in anhydrous toluene at reflux for 7 h (Scheme 1 and Table 1, entry 1) or at 110 °C under microwave irradiation for 20 min (Table 1, entry 2) gave rise to the formation of the piperidin-2-one **3a** in 38 and 50% yields, respectively, and occurs with full *exo* selectivity in analogy to the already reported results by Ghosez's group, some of which are supported by X-ray structure determination.[33–35] Since better yields were ob-

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tained when using the MAOS technique, this procedure was adopted for all of the examples reported in Table 1. As previously indicated, the *trans* relationship between the 5- and 6-positions is observed.[33–35] The structural relationship between the substituents in the 5- and 6-positions of the piperidin-2-one ring has been confirmed by an X-ray diffraction study, which was carried out to unequivocally determine the correct structure of **3a**. This analysis shows that the piperidinone ring adopts a distorted half-chair conformation with the hydrogen atoms bound to C5 and C6 in the *trans* orientation [H5C5C6H6 torsion angle of 176(1)°; see Figure 1]. In addition π–π interactions are present between the two phenyl rings. Moreover, the sole cyclic product obtained is that arising from a [4+2] HDA reaction, although in moderate–low yields (Table 1).

Table 1. Synthesis of piperidin-2ones **3a**–**e**.

Entry	Diene	X	Ar	Yield
1[a]	**1a**	H	Ph	**3a** (38%)
2[b]	**1a**	H	Ph	**3a** (50%)
3[b]	**1b**	H	*p*-$MeOC_6H_4$	**3b** (26%)
4[b]	**1c**	H	*p*-$O_2NC_6H_4$	**3c** (13%)
5[b]	**1d**	H	thienyl	**3d** (25%)
6[b]	**1e**	H	3-pyridyl	**3e** (18%)

[a] Convective heating. [b] Dielectric heating.

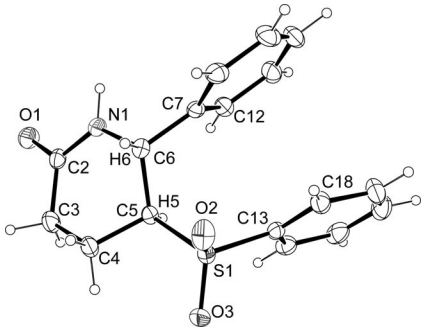
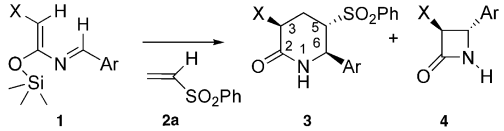


Figure 1. X-ray crystal structure of **3a** with a partial atomic numbering scheme. The atomic displacement parameters are drawn at the 30% probability level.

Alternatively, when using azadienes **1f**–**h**, which are characterized by the presence of substituent X on the 4-position, β-lactam **4** is also detected in the crude reaction mixture (Scheme 2 and Table 2), independently of the reaction conditions adopted (convective or dielectric heating; Table 2, entries 1 and 2); thus, showing a competitive electrocyclization reaction of the diene itself with the formation of the corresponding β-lactam **4**.



Scheme 2. Reaction of azadienes **1f**–**h** with dienophile **2a**.

From a stereochemical point of view, the stereo relationship between the substituents in the 3- and 5- and 5- and 6-positions of the piperidine-2-one ring **3** are *trans*. Invariably, *trans* also is the stereo relationship of the substituents in the 3- and 4-positions of β-lactam **4**.

Table 2. Reaction of azadienes **1f**–**h** with dienophile **2a**.

Entry	Diene	X	Ar	Yield	Yield
1[a]	**1f**	Cl	Ph	**3f** (11%)	**4f** (30%)[12]
2[b]	**1f**	Cl	Ph	**3f** (17%)	**4f** (38%)
3[b]	**1g**	Br	Ph	**3g** (16%)	**4g** (42%)[12]
4[b]	**1h**	PhS	Ph	**3h** (3%)	**4h** (16%)[11]

[a] Convective heating. [b] Dielectric heating.

This competition between a [2+2] electrocyclic (EC) reaction and a [4+2] cycloaddition has been already observed by our group with the same diene scaffold and a carbonyl compound as a dienophile. Theoretical studies by density functional computations[36] showed that the competition between the formation of a perhydrooxazinone (arising from a [4+2] HDA reaction) and/or a β-lactam (arising from a [2+2EC] Staudinger reaction) is governed by a delicate interplay between temperature and the very nature of the substituents of the diene and dienophile. Similar computational studies have also been performed in the present case in which there is competition between piperidin-2-one **3f** and the β-lactam **4f** formation. The example given in entry 1 of Table 2, yielding compounds **3f** and **4f** (X = Cl, Ar = Ph), was used as a model example. To have the most complete overview of the reaction profile, we examined, from a theoretical point of view, possible stereo relationships of the substituents for both the 5–6 *cis* (arising from *endo* attack) and 5–6 *trans* (arising from *exo* attack) compounds. Figure 2 shows the energy profiles, Figure 3 shows the geometries of the corresponding transition states and Figure 4 shows the variation of the $\Delta G^{\ddagger}$ energy barriers versus temperature. From Figure 2 it may anticipated that the HDA reaction is favoured over the [2+2EC] ring closure. In particular, the HDA *exo1* approach has the lowest energy barrier (Figure 2). However, careful analysis of Figure 4 shows that, on the basis of the variation of the $\Delta G^{\ddagger}$ barriers, the formation of the β-lactam is possible only at high temperatures. As a matter of fact, from an experimental point of view, the formation of the β-lactam ring takes place in toluene at reflux temperature (110 °C), whereas at 25 °C only traces of the six-membered ring are detected by NMR spectroscopic analysis after 5 h. The slope of the data in Figure 4, obtained by linear regression, indicates that the

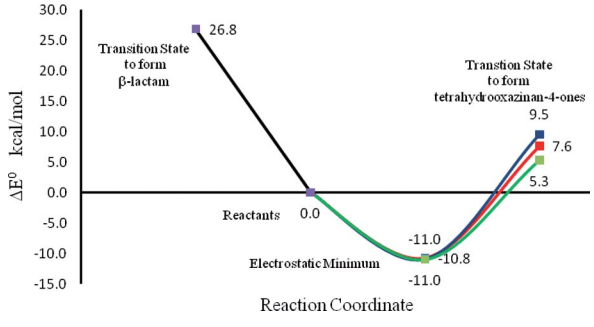


Figure 2. ΔE^0 energy profiles for the [2+2EC] (black line), *exo1* (green line), *endo1* (red line) and *endo2stack* (blue line) pathways.

exo1 reaction is higher in energy than electrocyclic closure (0.048 against 0.0035), and that the two lines intersect at 488 K. This intersection temperature indicates qualitatively when the mechanism changes; thus, suggesting that it is only possible to obtain the β-lactam product at high temperatures. Figure 2 shows the energy profiles of the two possible *endo* pathways, which have been called respectively *endo1* (**C**), and *endo2stack* (**B**) (Figure 3). *Endo2stack* (**B**) is due to the stacking interaction between the phenyl group of the diene with the phenyl group of the $-SO_2Ph$ substituent of the dienophile (see the corresponding transition-state geometries shown in Figure 3).

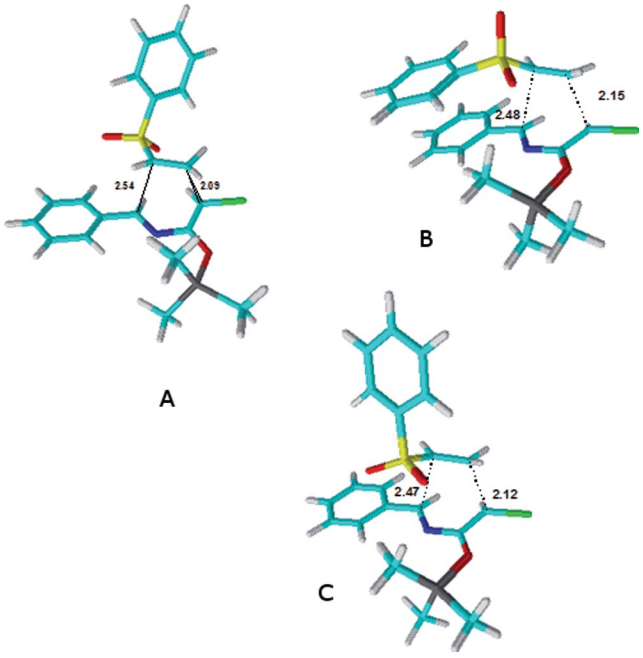


Figure 3. Optimized transition-state geometries for (A) *exo1*, (B) *endo2stack* and (C) *endo1* mechanisms.

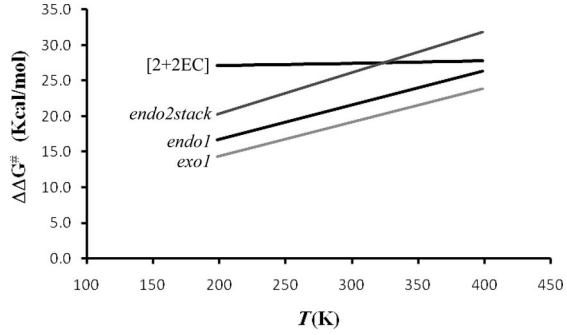
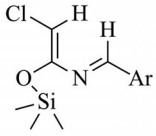
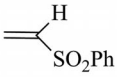
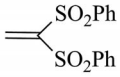


Figure 4. Variation of the $\Delta G^{\ddagger}$ energy barriers of the [2+2EC] (black line) and HDA reactions against temperature.

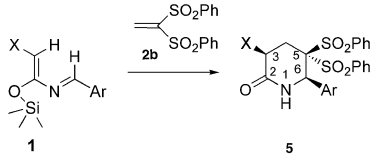
Of the three different electrostatic minima with almost identical energies, the *exo1* (**A**) (Figure 3) approach is favoured over both *endo* pathways. Of the *endo* pathways, the *endo2stack* (**B**) approach has a slightly higher barrier than that of *endo1* (**C**). The stabilizing stacking interaction probably does not compensate for the strain produced in molecule to maximize the non-bonded interaction. In fact, linear regression of the $\Delta G^{\ddagger}$ data in Figure 4 shows that *endo2stack* (**B**) has a higher slope (0.06) than *exo1* (**A**) and *endo1* (**C**) (ca. 0.048) due to a destabilizing entropy effect.[37]

Taking advantage of the results reported by De Lucchi and Pasquato[38] on the reactivity of sulfones in the Diels–Alder reaction, the next step in our studies was to consider a new reaction pathway in which the electron-demanding nature of the dienophile was increased by adding an extra sulfone group to the scaffold. To support this choice and before studying the mechanism from a theoretical point of view, we analyzed the global electrophilic indices of **1f**, **2a** and **2b** through conceptual DFT descriptors.[37,39,40] The results of this theoretical investigation have been reported in Table 3.

Table 3. Electrophilic indices of **1f**, **2a** and **2b**.

	 **1f**	 **2a**	 **2b**
μ	0.15	0.17	0.18
χ	3.99	4.65	4.89
η	0.22	0.31	0.28
S	4.47	3.25	3.55
ΔN_{max}	0.66	0.55	0.64
ω	1.31	1.29	1.56
$\Delta\omega$		–0.02	0.25

Both dienophiles **2a** and **2b** have a high ω index, but **2b** is higher than **2a**, and consequently, dienophile **2b** should have better reactivity in the HDA reaction and the formation of the β-lactam side product should be disfavoured. This result has been tested from a theoretical point of view by investigating the reaction of diene **1f** with dienophile **2b** (Scheme 3). For this reaction, we detected two different HDA transition states: *no-stack1* and *stack1* (see Figure 5 for the geometries of the corresponding transition states). Because *stack1*, which has the corresponding stacking interaction to that described in the **1f** + **2a** reaction, is not favoured due to a destabilizing entropy effect, we limit our discussion to the *no-stack1* pathway. The energy profile of the *no-stack1* mechanism is reported in Figure 6, together with the 2+2EC pathway. Figure 7 shows the variation of the $\Delta G^{\ddagger}$ energy barrier of the *no-stack1* reaction with temperature. Figure 6 shows that the HDA pathway is even more stabilized than that of the 2+2EC mechanism. This disulfone system forms an electrostatic minimum stabilized



Scheme 3. Reaction of azadienes **1** with dienophile **2b**.

by 11.7 kcal mol^{-1}. The energy barrier to form the HDA product is now half that of the monosulfone (8.7 versus 16.3 kcal mol^{-1}), which is lower than stabilization due to the electrostatic interaction.

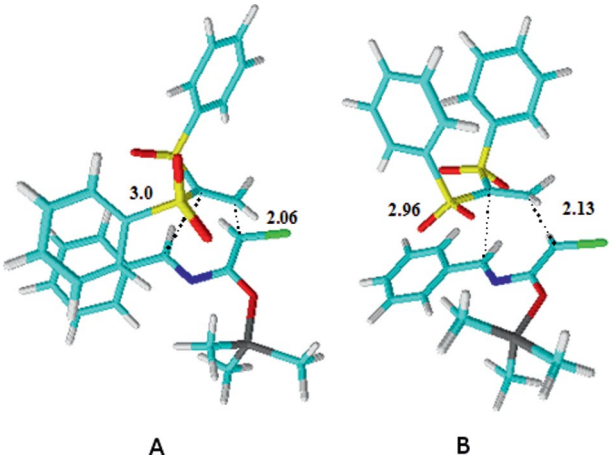


Figure 5. Optimized transition-state geometries for the (A) *stack1* and (B) *no-stack1* mechanisms.

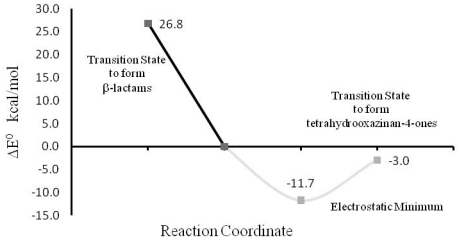


Figure 6. ΔE^0 energy profiles for the [2+2EC] (black line) and *no-stack1* (grey line) pathways.

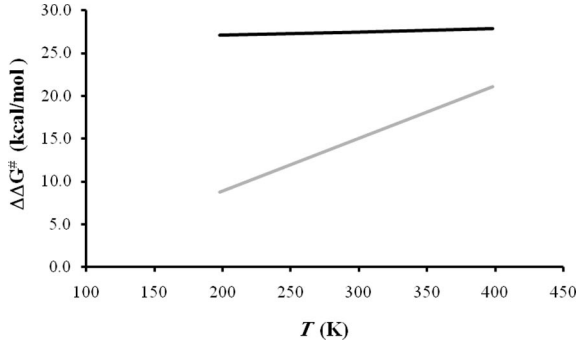


Figure 7. Variation of the $\Delta G^{\ddagger}$ energy barriers of the [2+2EC] (black line) and HDA *no-stack1* (grey line) reactions against temperature.

Figure 7 shows that, despite *no-stack1* having a higher slope (ca. 0.06), the intersection temperature becomes 524 K. In other words, this qualitative diagram indicates that a higher temperature is necessary to form the β-lactam.

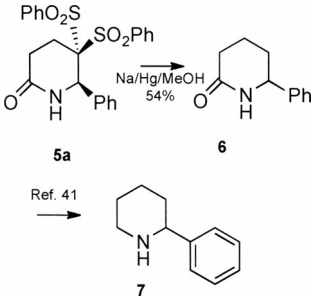
Bearing the results from the theoretical simulations in mind, we increased the reactivity of the dienophile by introducing a second sulfone moiety into the vinylsulfone scaffold (Scheme 3).

As predicted, a higher yielding HDA reaction took place and no traces of β-lactam compounds were present in the crude reaction mixture (Scheme 3 and Table 4).

Table 4. Synthesis of piperydin-2-ones **5** from azadienes **1** and dienophile **2b**.

Entry	Diene	R	Ar	Yield	Yield
1	**1a**	H	Ph	**5a** (61%)	**4a** (0%)
2	**1c**	H	*p*-$O_2NC_6H_4$	**5c** (30%)	**4c** (0%)
3	**1d**	H	thienyl	**5d** (38%)	**4d** (0%)
4	**1e**	H	3-pyridyl	**5e** (75%)	**4e** (0%)
5	**1f**	Cl	Ph	**5f** (64%)	**4f** (0%)
6	**1h**	Ph-S-	Ph	**5h** (25%)	**4h** (0%)
7	**1i**	Cl	*p*-FC_6H_4	**5i** (96%)	**4i** (0%)

Once again the stereo relationship between the substituents on the 3- (if present) and 6-positions (piperidine numbering) was a mutual *cis* relationship, as dictated by the HDA mechanism. To test the practicability and synthetic utility of the protocol reported herein, the elaboration of compound **5a** into the racemic (±)-2-phenylpiperidine (**7**) was explored and proved to be relatively straightforward (Scheme 4). The protocol to elaborate **5a** into **6**[41] was achieved through desulfonation with sodium amalgam in methanol. Elaboration of **6** into **7** with $LiAlH_4$ has already been reported.[41]



Scheme 4. Synthesis of 2-phenylpiperidine (**7**).

Conclusions

From the results reported, we have demonstrated that the reactivity of azadienes **1** may be extended to the preparation of an important scaffold: piperidine. Application of this strategy to the preparation of other biologically important compounds, with different functionalities on the ring, is currently under study. Theoretical studies were used to disclose the main parameters that favoured the [4+2] HDA reaction over the competitive [2+2 EC] reaction.

Experimental Section

General: All of the reactions were conducted under an N_2 atmosphere. NMR spectra were recorded with a Varian instrument at 400 (^{1}H) and 100 MHz (^{13}C). Chemical shifts (δ) for ^{1}H and ^{13}C NMR spectra and are reported in ppm; *J* values are reported in Hz. All chemical shifts are quoted relative to deuterated solvent signals. Optical rotations were measured at 25 °C with a Perkin–

Elmer Polarimeter 141. Mass spectra were recorded with a Finnigan MAT GCQ spectrometer in the electron impact mode at 70 eV and are reported as *m*/*z*. The infrared spectra were recorded with a Perkin–Elmer Spectrum BX spectrometer; wavenumbers are reported in cm^{-1}. Elemental analyses were performed at the CNR-ISMAR, Bologna, Italy. Solvents were distilled and dried according to standard procedures.

Reaction of Azadiene 1a with Sulfone 2a. Convective Heating (Table 1, entry 1): Azadiene **1a** (1 mmol) was dissolved in anhydrous toluene (10 mL) and **2a** (0.17 g, 1 mmol) was added in one portion with magnetic stirring. The solution was warmed at reflux temperature for 7 h then cooled to room temperature. The solvent was removed in vacuo and the crude reaction mixture was purified by recrystallization with ethanol to give **3a** (0.12 g, 38%).

Reaction of Azadiene 1a with Sulfone 2a. MAOS Conditions (Table 1, entry 2): Azadiene **1a** (1 mmol) was dissolved in anhydrous toluene (10 mL) and was put in a flask for microwave oven synthesis (Milestone). Sulfone **2a** (0.17 g, 1 mmol) was added and the mixture was submitted to microwave irradiation for 20 min at 500 W. The solvent was evaporated and **3a** was obtained by recrystallization of the crude reaction mixture with ethanol (0.16 g, 50%).

(5*S,6*R**)-6-Phenyl-5-(phenylsulfonyl)piperidin-2-one (3a):** White solid; m.p. 229 °C. IR ($CHCl_3$): 1668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (m, 2 H, Ar), 7.62 (m, 1 H, Ar), 7.16 (m, 2 H, Ar), 7.27 (m, 3 H, Ar), 7.12 (m, 2 H, Ar), 5.73 (br. s, 1 H, NH), 5.15 (dd, J_1 = 3.2, J_2 = 4.4 Hz, 1 H, 6-H), 3.42 (q, J = 5.6 Hz, 1 H, 5-H), 2.79 (dt, J_1 = 8.0, J_2 = 18.0 Hz, 1 H, 3-H_A), 2.48 (dt, J_1 = 6.4, J_2 = 18.0 Hz, 1 H, 3-H_B), 2.22 (m, 2 H, 4-CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.54, 139.77, 137.62, 134.09, 129.41, 129.11, 126.87, 128.53, 126.44, 63.76, 55.20, 28.05, 18.47 ppm. MS: *m*/*z* = 316, 174, 173, 158, 144. $C_{17}H_{17}NO_3S$ (315.09): calcd. C 64.74, H 5.43, N 4.44; found C 64.80, H 5.44, N 4.44.

X-ray Crystallography for 3a: The X-ray intensity data for **3a** were measured on a Bruker SMART Apex II diffractometer equipped with a CCD area detector using a graphite-monochromated Mo-K_α radiation source (λ = 0.71073 Å). Cell dimensions and the orientation matrix were initially determined from a least-squares refinement on reflections measured in 3 sets of 20 exposures, collected in 3 different ω regions and eventually refined against all data. For the crystal, a full sphere of reciprocal space was scanned by 0.3° ω steps. The software SMART[45] was used for collecting frames of data, indexing reflections and determining lattice parameters. The collected frames were then processed for integration by SAINT software[45] and an empirical absorption correction was applied with SADABS.[46] The structure was solved by direct methods (SIR 97)[47] and subsequent Fourier syntheses and refined by full-matrix least-squares calculations on F^2 (SHELXTL),[48] attributing anisotropic thermal parameters to the non-hydrogen atoms. All hydrogen atoms were located in the Fourier map. The methylene and aromatic hydrogen atoms were placed in calculated positions and refined with isotropic thermal parameters U(H) = 1.2 U_{eq}(C), and allowed to ride on their carrier carbons, whereas the methine and aminic hydrogen atoms were located in the Fourier map and refined isotropically.

$C_{17}H_{17}NO_3S$, M_r = 315.38, monoclinic, space group $P2_1/c$ (no. 14); a = 15.9096(11), b = 5.7746(4), c = 17.2601(12) Å, β = 17.2601(12)°, V = 1516.49(18) $Å^3$, Z = 4; T = 293(2) K, $\rho_{calcd.}$ = 1.381 $g\,cm^{-1}$, μ(Mo-K_α) = 0.226 mm^{-1}, F(000) = 664, crystal size: 0.20 × 0.25 × 0.05 mm, 16370 reflections collected [R(int) = 0.0353], 3707 unique. Final $R[I > 2\sigma(I)]$ = 0.0402, $wR2[I > 2\sigma(I)]$ = 0.0937, and for all data R(all data) = 0.0643, $wR2$(all data) = 0.1055.

CCDC-829176 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for the Reaction of Azadienes 1b–h with Sulfone 2a under MAOS Conditions: Azadiene **1b**–**h** (1 mmol) was dissolved in anhydrous toluene (10 mL) and was put in a flask for microwave oven synthesis (Milestone). Sulfone **2a** (0.17 g, 1 mmol) was added and the mixture was submitted to microwave irradiation for 20 min at 500 W. The solvent was evaporated and the residue was purified by flash chromatography (eluent CH_2Cl_2/ethyl acetate, 75:25) to afford products **3b**–**h** and β-lactams **4f**–**h** in the yields and ratios reported in Tables 1 and 2.

(5*S,6*R**)-6-(4-Methoxyphenyl)-5-(phenylsulfonyl)piperidin-2-one (3b):** White solid; m.p. 160–165 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (m, 2 H, Ar), 7.59 (m, 1 H, Ar), 7.46 (m, 2 H, Ar), 6.97 (d, J = 8.8 Hz, 2 H, Ar), 6.72 (d, J = 8.8 Hz, 2 H, Ar), 6.48 (br. s, 1 H, NH), 5.01 (dd, J_1 = 1.6, J_2 = 4.4 Hz, 1 H, 6-H), 3.72 (s, 3 H, OMe), 3.36 (dt, J_1 = 4.8, J_2 = 6.0 Hz, 1 H, 5-H), 2.70 (m, 1 H, 3-H_A), 2.40 (m, 1 H, 3-H_B), 2.16 (m, 2 H, 4-CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.63, 159.49, 137.68, 133.81, 131.51, 129.21, 128.35, 127.64, 114.21, 63.78, 55.20, 54.60, 28.06, 18.41 ppm. MS: *m*/*z* = 345, 329, 203, 188, 172, 134, 92, 77. $C_{18}H_{19}NO_4S$ (345.10): calcd. C 62.59, H 5.54, N 4.06; found C 62.55, H 5.55, N 4.05.

(5*S,6*R**)-6-(4-Nitrophenyl)-5-(phenylsulfonyl)piperidin-2-one (3c):** Yellow solid; m.p. 225–230 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, J = 8.8 Hz, 2 H, Ar), 7.84 (d, J = 8.8 Hz, 2 H, Ar), 7.69 (m, 1 H, Ar), 7.56 (m, 2 H, Ar), 7.39 (m, 2 H, Ar), 6.41 (br. s, 1 H, NH), 5.31 (dd, J_1 = 2.4, J_2 = 4.4 Hz, 1 H, 6-H), 3.38 (dt, J_1 = 4.8, J_2 = 6.8 Hz, 1 H, 5-H), 2.77 (m, 1 H, 3-H_A), 2.47 (m, 1 H, 3-H_B), 2.24–2.08 (m, 2 H, 4-CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.52, 147.97, 147.02, 137.05, 134.51, 129.63, 128.59, 127.70, 124.30, 63.58, 54.58, 28.06, 19.07 ppm. MS: *m*/*z* = 360, 359, 299, 227, 218, 201, 171, 115, 91, 78. $C_{17}H_{16}N_2O_5S$ (360.08): calcd. C 56.60, H 4.47, N 7.77; found C 56.85, H 4.48, N 7.79.

(5*S,6*R**)-5-(Phenylsulfonyl)-6-(thiophen-3-yl)piperidin-2-one (3d):** Yellow solid; m.p. 190 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (m, 2 H, Ar), 7.64 (m, 1 H, Ar), 7.53 (m, 2 H, Ar), 7.18 (m, 1 H, Th), 6.86 (m, 2 H, Th), 6.29 (br. s, 1 H, NH), 5.38 (dd, J_1 = 2.8, J_2 = 4.8 Hz, 1 H, 6-H), 3.50 (ddd, J_1 = J_2 = 4.8, J_3 = 6.8 Hz, 1 H, 5-H), 2.73 (m, 1 H, 3-H_A), 2.45 (m, 1 H, 3-H_B), 2.38–2.20 (m, 2 H, 4-CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.16, 143.79, 137.62, 134.11, 129.40, 128.52, 127.13, 126.18, 125.99, 64.35, 51.37, 28.21, 19.00 ppm. MS: *m*/*z* = 321, 305, 179, 164, 150, 110. $C_{15}H_{15}NO_3S_2$ (321.05): calcd. C 56.05, H 4.70, N 4.36; found C 56.22, H 4.68, N 4.37.

(5*S,6R*)-5-(Phenylsulfonyl)-6-(pyridin-3-yl)piperidin-2-one (3e):** White solid; m.p. 205 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1674 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.55 (d, J = 2.0 Hz, 1 H, Py), 8.53 (dd,, J_1 = 1.6, J_2 = 4.8 Hz, 1 H, Py), 7.80 (m, 2 H, Ar), 7.70 (m, 1 H, Py), 7.66 (m, 1 H, Ar), 7.53 (m, 1 H, Ar), 7.33 (dd, J_1 = 5.2, J_2 = 8.0 Hz, 1 H, Py), 6.34 (br. s, 1 H, NH), 5.20 (dd, J_1 = 2.0, J_2 = 6.4 Hz, 1 H, 6-H), 3.52 (q, J = 6.4 Hz, 1 H, 5-H), 2.75 (m, 1 H, 3-H_A), 2.52 (m, 1 H, 3-H_B), 2.22 (m, 2 H, 4-CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.50, 149.47, 148.07, 137.29, 134.83, 134.34, 129.57, 128.51, 123.89, 63.47, 53.43, 28.34, 19.15 ppm. MS: *m*/*z* = 316, 175, 141, 78. $C_{16}H_{16}N_2O_3S$ (316.09): calcd. C 60.74, H 5.10, N 8.85; found C 60.56, H 5.12, N 8.87.

(3*S,5*S**,6*R**)-3-Chloro-6-phenyl-5-(phenylsulfonyl)piperidin-2-one (3f):** White solid; m.p. 150 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1686 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (m, 2 H, Ar), 7.57 (m, 1 H, Ar), 7.43 (m, 2 H, Ar), 7.25 (m, 3 H, Ar), 7.16 (m, 2 H, Ar), 5.98 (br. s, 1 H, NH), 5.03 (dd, J_1 = 1.6, J_2 = 7.2 Hz, 1 H, 6-H), 4.71 (t, J = 5.2 Hz, 1 H, 3-H), 3.87 (ddd, J_1 = 4.4, J_2 = 7.2, J_3 = 8.8 Hz, 1 H, 5-H), 2.67 (m, 2 H, 4-CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.03, 138.39, 137.42, 134.14, 129.34, 129.11, 129.05, 128.33, 127.13, 61.05, 56.43, 51.16, 29.43 ppm. MS: *m*/*z* = 349, 314, 258, 208, 158, 91, 77. $C_{17}H_{16}ClNO_3S$ (349.05): calcd. C 58.37, H 4.61, N 4.00; found C 58.19, H 4.59, N 4.02.

(3*S,5*S**,6*R**)-3-Bromo-6-phenyl-5-(phenylsulfonyl)piperidin-2-one (3g):** Yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (m, 2 H, Ar), 7.56 (m, 1 H, Ar), 7.40 (m, 2 H, Ar), 7.24 (m, 5 H, Ar), 6.20 (br. s, 1 H, NH), 5.04 (dd, J_1 = 2.0, J_2 = 8.4 Hz, 1 H, 6-H), 4.73 (t, J = 5.2 Hz, 1 H, 3-H), 3.97 (q, J_1 = 6.8 Hz, 1 H, 5-H), 2.72 (dd, J_1 = 5.2, J_2 = 6.8 Hz, 2 H, 4-CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.39, 138.23, 137.57, 134.02, 129.25, 129.15, 129.04, 128.24, 127.37, 61.23, 56.81, 40.67, 29.98 ppm. MS: *m*/*z* = 395, 393, 314, 254, 252, 141, 77. $C_{17}H_{16}BrNO_3S$ (393.00): calcd. C 51.79, H 4.09, N 3.55; found C 51.67, H 4.11, N 3.54.

(3*S,5*S**,6*R**)-6-Phenyl-5-(phenylsulfonyl)-3-(phenylthio)piperidin-2-one (3h):** Yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (m, 2 H, Ar), 7.61 (m, 1 H, Ar), 7.46 (m, 2 H, Ar), 7.34 (m, 4 H, Ar), 7.20 (m, 4 H, Ar), 6.95 (m, 2 H, Ar), 6.42 (br. s, 1 H, NH), 5.07 (dd, J_1 = 2.4, J_2 = 5.6 Hz, 1 H, 6-H), 4.19 (dd, J_1 = 5.6, J_2 = 8.0 Hz, 1 H, 3-H), 3.65 (ddd, J_1 = 4.4, J_2 = 5.6, J_3 = 7.2 Hz, 1 H, 5-H), 2.44 (ddd, J_1 = 5.6, J_2 = 7.2, J_3 = 12.4 Hz, 1 H, 4-H_A), 2.32 (ddd, J_1 = 4.4, J_2 = 8.0, J_3 = 12.4 Hz, 1 H, 4-H_B) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.85, 139.07, 137.33, 134.66, 134.08, 133.23, 129.37, 129.32, 128.99, 128.79, 128.64, 128.42, 126.69, 62.36, 55.53, 45.31, 25.77 ppm. MS: *m*/*z* = 423, 326, 281, 248, 204, 172, 144, 129, 91, 77. $C_{23}H_{21}NO_3S_2$ (423.10): calcd. C 65.22, H 5.00, N 3.31; found C 65.48, H 5.02, N 3.30.

General Procedure for the Reaction of Azadienes 1a,c–f,h,i with Sulfone 2b under MAOS Conditions: Azadiene **1a**,**c**–**f**,**h**,**i** (1 mmol) was dissolved in anhydrous toluene (10 mL) and was put in a flask for microwave oven synthesis (Milestone). Sulfone **2b** (0.31 g, 1 mmol) was added and the mixture was submitted to microwave irradiation for 20 min at 500 W. The solvent was evaporated and the residue was purified by flash chromatography (eluent CH_2Cl_2/ethyl acetate, 80/20) to afford the products **5 a**,**c**–**f**,**h**,**i**.

6-Phenyl-5,5-bis(phenylsulfonyl)piperidin-2-one (5a): M.p. 218 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1641 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (m, 2 H, Ar), 7.76 (m, 1 H, Ar), 7.64 (m, 2 H, Ar), 7.55 (m, 1 H, Ar), 7.48 (m, 2 H, Ar), 7.36–7.22 (m, 7 H, Ar), 6.53 (br. s, 1 H, NH), 5.25 (d, J = 3.6 Hz, 1 H, 6-H), 2.94 (m, 3 H, 3-CH_2, 4-H_A), 2.80 (m, 1 H, 4-H_B) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.62, 138.41, 136.99, 136.23, 135.19, 134.12, 131.27, 130.67, 130.20, 129.17, 128.44, 128.31, 90.24, 58.48, 27.74, 23.36 ppm. MS: *m*/*z* = 454, 313, 171, 143, 115, 95, 77. $C_{23}H_{21}NO_5S_2$ (455.09): calcd. C 60.64, H 4.65, N 3.05; found C 60.47, H 4.67, N 3.05.

6-(4-Nitrophenyl)-5,5-bis(phenylsulfonyl)piperidin-2-one (5c): White solid; m.p. 160 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (m, 4 H, Ar), 7.80 (m, 1 H, Ar), 7.73 (m, 2 H, Ar), 7.67 (m, 3 H, Ar), 7.49 (m, 4 H, Ar), 6.74 (br. s, 1 H, NH), 5.28 (d, J = 2.8 Hz, 1 H, 6-H), 3.05 (m, 1 H, 3-H_A), 2.86 (m, 3 H, 4-CH_2, 3-H_B) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.83, 148.17, 143.22, 138.18, 136.24, 135.61, 134.86, 131.15, 130.99, 130.98, 129.52, 128.58, 123.40, 89.71, 57.95, 29.69, 23.47 ppm. MS: *m*/*z* = 499, 438, 359, 218, 78. $C_{23}H_{20}NO_7S_2$ (500.07): calcd. C 55.19, H 4.03, N 5.60; found C 55.39, H 4.01, N 5.62.

5,5-Bis(phenylsulfonyl)-6-(thiophen-2-yl)piperidin-2-one (5d): White solid; m.p. 225 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, J = 7.2 Hz, 2 H, Ar), 7.73 (m, 3 H, Ar), 7.62 (m, 3 H, Ar), 7.45 (m, 2 H, Ar), 7.29 (d, J = 5.2 Hz, 1 H, Th), 7.17 (d, J = 3.6 Hz, 1 H, Th), 6.92 (dd, J_1 = 3.6, J_2 = 5.2 Hz, 1 H, Th), 6.12 (br. s, 1 H, NH), 5.55 (d, J = 3.2 Hz, 1 H, 6-H), 3.05 (m, 1 H, 3-H_A), 2.83 (m, 1 H, 3-H_B), 2.76 (m, 2 H, 4-CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.64, 138.68, 138.46, 136.89, 135.29, 134.42, 131.32, 130.93, 130.72, 129.26, 128.48, 127.99, 126.53, 89.75, 54.64, 29.69, 24.40 ppm. MS: *m*/*z* = 461, 369, 351, 319, 254, 177, 153, 135, 125, 111, 97, 77. $C_{21}H_{19}NO_5S_3$ (461.04): calcd. C 54.64, H 4.15, N 3.03; found C 54.45, H 4.14, N 3.05.

5,5-Bis(phenylsulfonyl)-6-(pyridin-3-yl)piperidin-2-one (5e): White solid; m.p. 215 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.55 (dd, J_1 = 2.0, J_2 = 4.8 Hz, 1 H, Py), 8.51 (d, J = 2.0 Hz, 1 H, Py), 8.16 (m, 2 H, Ar), 7.79 (m, 1 H, Ar), 7.72 (m, 1 H, Py), 7.66 (m, 5 H, Ar), 7.45 (m, 2 H, Ar), 7.23 (dd, J_1 = 4.8, J_2 = 8.0 Hz, 1 H, Py), 6.26 (br. s, 1 H, NH), 5.25 (d, J = 3.2 Hz, 1 H, 6-H), 2.98 (m, 1 H, 3-H_A), 2.88 (m, 1 H, 3-H_B), 2.82 (m, 2 H, 4-CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.24, 150.41, 149.29, 145.21, 137.91, 136.36, 135.40, 134.62, 132.73, 131.04, 130.70, 129.29, 128.51, 123.34, 89.30, 56.02, 27.40, 23.32 ppm. MS: *m*/*z* = 456, 315, 174, 77. $C_{22}H_{20}N_2O_5S_2$ (456.08): calcd. C 57.88, H 4.42, N 6.14; found C 57.70, H 4.43, N 6.17.

(3*S,6*R**)-3-Chloro-6-phenyl-5,5-bis(phenylsulfonyl)piperidin-2-one (5f):** White solid; m.p. 155 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.21 (m, 2 H, Ar), 7.80 (m, 1 H, Ar), 7.68 (m, 2 H, Ar), 7.59 (m, 1 H, Ar), 7.52 (m, 2 H, Ar), 7.40 (m, 2 H, Ar), 7.31 (m, 1 H, Ar), 7.26 (m, 4 H, Ar), 6.68 (d, J = 3.6 Hz, 1 H, NH), 5.14 (d, J = 3.6 Hz, 1 H, 6-H), 4.99 (dd, J_1 = 8.0, J_2 = 10.4 Hz, 1 H, 3-H), 3.50 (dd, J_1 = 8.0, J_2 = 14.8 Hz, 1 H, 4-H_A), 3.30 (dd, J_1 = 10.4, J_2 = 14.8 Hz, 1 H, 4-H_B) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.30, 137.91, 136.03, 135.61, 135.13, 134.45, 131.34. 130.64, 130.15, 129.47, 129.38, 128.64, 128.53, 90.50, 58.85, 50.22, 33.49 ppm. MS: *m*/*z* = 490, 453, 349, 312, 246, 207, 181, 146, 77. $C_{23}H_{20}ClNO_5S_2$ (489.05): calcd. C 56.38, H 4.11, N 2.86; found C 56.54, H 4.11, N 2.86.

(3*S,6*R**)-6-Phenyl-5,5-bis(phenylsulfonyl)-3-(phenylthio)piperidin-2-one (5h):** White solid; m.p. 210 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.20 (m, 2 H, Ar), 7.77 (m, 1 H, Ar), 7.64 (m, 2 H, Ar), 7.57 (m, 2 H, Ar), 7.49 (m, 1 H, Ar), 7.38 (m, 1 H, Ar), 7.27 (m, 3 H, Ar), 7.21 (m, 3 H, Ar), 6.99 (m, 3 H, Ar), 6.61 (m, 2 H, Ar), 6.23 (d, J = 3.2 Hz, 1 H, NH), 5.29 (d, J = 3.2 Hz, 1 H, 6-H), 4.38 (dd, J_1 = 7.2, J_2 = 12.0 Hz, 1 H, 3-H), 3.29 (dd, J_1 = 7.2, J_2 = 14.4 Hz, 1 H, 4-H_A), 2.78 (dd, J_1 = 12.0, J_2 = 14.4 Hz, 1 H, 4-H_B) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.40, 137.43, 137.31, 136.09, 135.29, 135.25, 133.85, 131.58, 130.70, 130.44, 130.25, 129.33, 129.18, 129.15, 129.08, 128.46, 128.32, 90.86, 58.89, 44.44, 30.93 ppm. MS: *m*/*z* = 563, 421, 369, 343, 312, 280, 246, 171, 143, 110, 95, 78. $C_{29}H_{25}NO_5S_3$ (563.09): calcd. C 61.79, H 4.47, N 2.48; found C 61.58, H 4.48, N 2.48.

(3*S,6*R**)-3-Chloro-6-(4-fluorophenyl)-5,5-bis(phenylsulfonyl)-piperidin-2-one (5i):** White solid; m.p. 200 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (m, 2 H, Ar), 7.98 (d, J = 3.6 Hz, 1 H, NH), 7.74 (m, 1 H, Ar), 7.63 (m, 2 H, Ar), 7.55 (m, 3 H, Ar), 7.40 (m, 2 H, Ar), 7.23 (m, 2 H, Ar), 6.90 (m, 2 H, Ar), 5.18 (d, J = 3.6 Hz, 1 H, 6-H), 4.88 (dd, J_1 = 8.0, J_2 = 9.6 Hz, 1 H, 3-H), 3.50 (dd, J_1 = 8.0, J_2 = 14.8 Hz, 1 H, 4-H_A),

3.26 (dd, J_1 = 10.4, J_2 = 14.8 Hz, 1 H, 4-H_B) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.10, 161.61, 137.73, 135.49, 135.40, 134.41 131.86, 131.78, 131.14, 130.97, 130.94, 130.26, 129.27, 128.42, 115.39, 115.17, 89.99, 57.54, 49.91, 32.85 ppm. MS: *m*/*z* = 438 (M^+ = 508), 366, 349, 330, 264, 225, 199, 164, 150,125, 97, 77. $C_{23}H_{19}ClFNO_5S_2$ (507.04): calcd. C 54.38, H 3.77, N 2.76; found C 54.24, H 3.75, N 2.77.

Desulfonylation Procedure. Preparation of 6: Compound **5a** (0.11 g, 1 mmol) was dissolved in methanol (20 mL). KH_2PO_4 (210 mg) and sodium amalgam (Hg 0.44 g, Na 27 mg) were added and the reaction mixture was stirred at r.t. for 3 h. The mixture was filtered through a Celite pad and the solvent was removed in vacuo. The resulting crude mixture was purified by flash chromatography on silica gel (ethyl acetate/MeOH 95:5) to afford **6** in 54% yield. IR ($CHCl_3$): $\tilde{\nu}$ = 1654 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 2 H), 7.29 (m, 3 H), 5.98 (br. s, 1 H), 4.54 (dd, J_1 = 4.8, J_2 = 9.2 Hz, 1 H), 2.45 (m, 2 H), 2.10 (m, 1 H), 1.91 (m, 1 H), 1.80 (m,1 H), 1.68 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.39, 142.41, 128.83, 127.95, 126.04, 57.79, 32.12, 31.20, 19.63 ppm. MS: *m*/*z* = 175, 174, 146, 118, 104, 77. $C_{11}H_{13}NO$ (175.10): calcd. C 75.40, H 7.48, N 7.99; found C 75.32, H 7.44, N 7.85.

Computational Methods: Due to the presence of non-bonded interactions, DFT calculations were carried out by using the Truhlar's hybrid functional M062X[42] together with the 6-311+G(d,p)[43] basis set within the framework of the Gaussian 09 suite of programs.[44] All of the molecular structures were fully optimized by using the Berny analytical gradient optimization method and the stationary points were characterized by frequency calculation. The intrinsic reaction coordinate (IRC) was used to trace the path of the chemical reactions. Thermochemical analysis was performed at different temperatures (198.15, 298.15 and 398.15 K), starting from the frequency calculations. The electrophilicity indices were calculated at the B3LYP/6-31g* computational level to compare the values with the reported classification of electrophilicity.[37,39,40] The global index, ω, is given by the expression $\omega = \mu^2/2\eta$ in terms of the electronic chemical potential, μ, and the chemical hardness, η. The absolute electronegativity, χ, is the negative of the chemical potential, μ; the softness, S, is the inverse of the hardness and the ΔN_{max}, $-\mu/\eta$, is the maximum amount of electronic charge that the electrophile system may accept. These quantities were approximated by using the one-electron energies of the HOMO and LUMO frontier molecular orbitals, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_H - \varepsilon_L)/2$, respectively.

Supporting Information (see footnote on the first page of this article): Optimized structures and energies (a.u.) for monosulfone HDA and [2+2EC] reactions and for disulfone HDA and [2+2EC] reactions; DFT M062X 6-311+G(d,p) optimized structures.

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