

DIELS-ALDER REACTION OF THE *N*-PROTECTED 3-PHENYLTHIO-2(1*H*)-DIHYDROPYRIDINONE DERIVATIVES†

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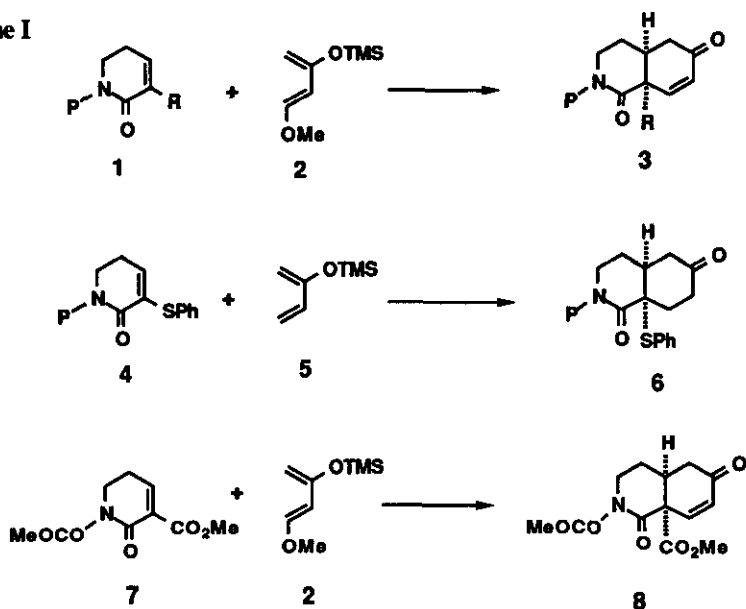
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Abstract- Efficient methods for the preparation of *N*-protected 3-phenylthio-2(1*H*)-dihydropyridinones from 2-piperidone and their Diels-Alder reaction with 2-trimethylsilyloxy-butadiene are described. The role of the electron-withdrawing *N*-protecting group in the dienophiles is rationalized in terms of the lowered energy level in LUMO.

During the course of our synthetic study on marine alkaloid manzamines,¹ it was proved that the Diels-Alder (D-A) reaction of 3-alkyldihydropyridinones (1) with Danishefsky diene (2) is an effective method to construct the functionalized *cis*-hydroisoquinoline skeleton such as 3.

† This paper is dedicated to Dr Arnord Brossi on the occasion of his 70th birthday.

Scheme I



As an extension of this tactic towards differently-assembled isoquinoline derivatives, we have now surveyed the D-A reactions of the 3-phenylthio-substituted dihydropyridinones (4).

It is noteworthy that Simpkins² has reported the related D-A reaction of 1,3-bis(methoxycarbonyl)-dihydropyridinone (7) with siloxydienes, which afforded the corresponding adduct (8) in high yield.

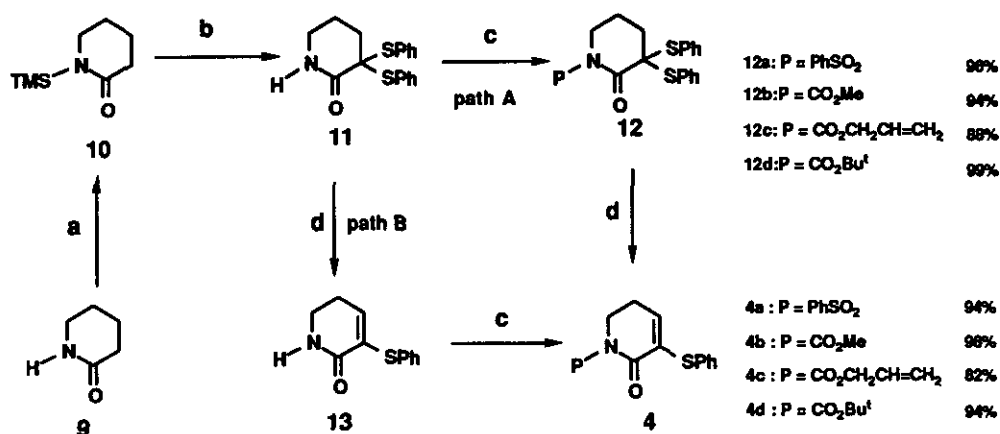
It is our aim here to clarify the reactivities of these dihydropyridinones in the D-A reaction and furthermore, to find more practical conditions for the D-A reaction of 4 with siloxydiene, thus furnishing another method for the construction of functionalized isoquinoline skeleton.

Preparation of the Dienophiles: 3-Phenylthio-2-dihydropyridinones

Based on our previous results on the D-A reaction of 3-alkyldihydropyridinones,¹ it is important to select a suitable *N*-protecting group of the dienophile. Experimental data and theoretical calculations indicate that electron-withdrawing groups are essential for the successful D-A reaction.

Thus, various 3-phenylthiodihydropyridinones (4) with different *N*-protecting groups (P) were prepared according to the general synthetic procedure shown in Scheme II.

Scheme II Preparation of the Dienophiles



Conditions: a) KN(TMS)₂, TMSCl, -78 °C; b) KN(TMS)₂, PhSSPh, -78 °C ~room temperature; c) Base, P-X, THF, -78 °C; d) 1) mCPBA, 0 °C; 2) benzene, reflux

3,3-Bis(phenylthio)-2-piperidone (**11**), the key intermediate for this transformation, was conveniently prepared from 2-piperidone (**9**) via *N*-TMS-2-piperidone (**10**)³. Attachment of electron-withdrawing groups such as PhSO₂, CO₂Me, CO₂CH₂CH=CH₂, and BOC (COOBu^t) to **11** was carried out in a conventional way using *n*-BuLi or KN(TMS)₂ as a base to afford **12** in good yield.

Finally **12** was treated with mCPBA followed by brief heating to furnish the desired dienophiles (**4**) in satisfactory yield. Through this sequence (path A), four different dienophiles (**4a**–**4d**) were prepared as shown in Scheme II. Another path (path B) is also available, which involves the initial oxidative elimination of phenylthio group to form **13** followed by the *N*-protection. These dienophiles are stable and fully characterized by spectroscopic means and elemental analysis.

Diels-Alder Reaction of 3-Phenylthio-2-dihydropyridinones

Having established an efficient method for the preparation of the required dienophiles (**4**), we began our investigation on the D-A reaction with 2-trimethylsilyloxybutadiene (**5**)⁴ to obtain hydroisoquinolinone derivatives such as **6**. We initially hoped that these 3-phenylthio substituted dihydropyridinones (**4**) would participate in cycloadditions more easily than previous 3-alkyldihydropyridinones (**1**).

Table I Diels-Alder Reaction of the Dihydropyridinone Derivatives

Reaction scheme: A dihydropyridinone derivative (4) with a substituent P at the nitrogen and a substituent SPh at the 2-position reacts with a siloxydiene (5) in the presence of a Lewis acid to form a bicyclic intermediate. This intermediate is then treated with H₃O⁺ to yield the final product (6), which is a bicyclic dihydropyridinone with a ketone group at the 4-position and a substituent SPh at the 2-position.

Run	4	P	Lewis Acid	solvent	temp	time	results
1	a	SO ₂ Ph	—	<i>p</i> -cymene	180 °C	6 h	NR
2	a	SO ₂ Ph	ZnBr ₂ (1 eq.)	CH ₂ Cl ₂	room temperature	24 h	83%
3	b	CO ₂ Me	—	<i>p</i> -cymene	180 °C	6 h	NR
4	b	CO ₂ Me	EtAlCl ₂ (1 eq.)	toluene	room temperature	2 h	70%
5	c	CO ₂ CH ₂ CH=CH ₂	—	<i>p</i> -cymene	180 °C	6 h	NR
6	c	CO ₂ CH ₂ CH=CH ₂	ZnBr ₂ (1 eq.)	CH ₂ Cl ₂	room temperature	24 h	NR
7	c	CO ₂ CH ₂ CH=CH ₂	EtAlCl ₂ (1 eq.)	toluene	room temperature	24 h	10%
8	c	CO ₂ CH ₂ CH=CH ₂	EtAlCl ₂ (2 eq.)	toluene	room temperature	15 min	80%
9	c	CO ₂ CH ₂ CH=CH ₂	EtAlCl ₂ (2 eq.)	CH ₂ Cl ₂	room temperature	24 h	20%
10	d	BOC	EtAlCl ₂ (1 eq.)	toluene	room temperature	1 h	N-deprotection

In contrast to our expectation, however, no D-A adducts were obtained from the reaction of these dienophiles under thermal conditions (Runs 1, 3, 5). We next turned our attention to the D-A reaction with a Lewis acid catalyst.

The results of these D-A reactions are summarized in Table I. It was found that zinc bromide and ethylaluminum dichloride are suitable catalysts for our D-A reaction.

Thus, in the presence of ZnBr₂ (1 equiv.), the *N*-PhSO₂ dienophile (4a) was treated with excess siloxydiene (5) at room temperature for 24 h followed by an acid treatment to afford *cis*-hydroisoquinolinone (6) in 83% yield (Run 2). On the other hand, the reaction of the *N*-CO₂Me dienophile (4b) proceeded much faster by the aid of EtAlCl₂ (2 equiv.) in toluene to give 70% yield (Run 4). However, partial deprotection of the *N*-COOMe by the acid catalyst occurred and the products consisted of both the usual D-A adduct (6, P=COOMe) and the *N*-deprotected adduct (6, P=H).

With a smaller amount of Lewis acid (1 ~ 0.3 equiv.), adducts (**6b**) were obtained only in ~20% yield and a large amount of unreacted dienophile was recovered. It was also found that ZnBr_2 is not effective for this substrate.

In the case of *N*-allyloxycarbonyl dienophile (**4c**), reaction did not proceed with ZnBr_2 catalyst (1 equiv.) in CH_2Cl_2 (Run 6), while EtAlCl_2 (2 equiv.) in toluene effectively promoted this reaction to form the desired adduct in 80% yield (Run 8). For this catalyst toluene was a better solvent than CH_2Cl_2 (Run 9). Partial deprotection was again accompanied and the products consisted of the usual D-A adduct (**6**, $\text{P}=\text{CO}_2\text{CH}_2\text{CH}=\text{CH}_2$) and the *N*-deprotected (NH) adduct (**6**, $\text{P}=\text{H}$).

Finally in the case of more labile *N*-BOC dienophile (**4d**), deprotection of the *N*-BOC group was the only reaction observed (Run 10) and no D-A adduct was obtained even though a weak Lewis acid such as $\text{BF}_3\cdot\text{Et}_2\text{O}$ was employed.

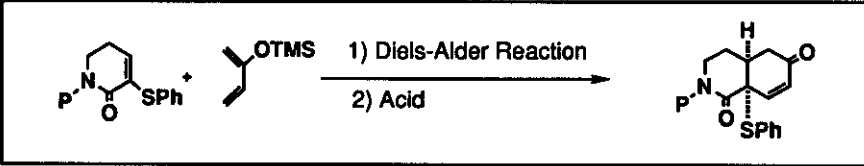
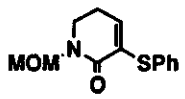
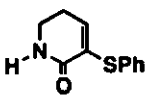
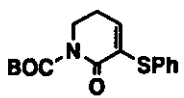
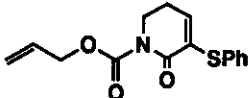
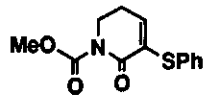
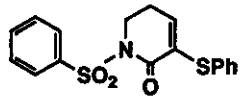
MO Calculation for the Dienophiles

In order to assess the effects of the *N*-protecting groups, MO calculations of these dienophiles were carried out according to the PM3 calculation program in MOPAC.⁵ The results are summarized in Table II, clearly showing the differences in the LUMO level. Thus, the *N*-alkyl (MOM) and NH dienophiles showed relatively higher energy levels of the LUMO and as a consequence, in these dienophiles no cycloaddition was observed. On the other hand, dienophiles which have electron-withdrawing protecting groups have relatively low energy levels in the LUMO and the desired cycloaddition reactions were observed.

In the case of the *N*- SO_2Ph dienophile (**4a**), the lowest LUMO level was attained and the highest isolated yield of D-A product (**6a**) obtained. These results are compatible with the previous case,¹ in which the dienophiles were 3-alkyldihydropyridinones (**1**).

In summary, Diels-Alder reaction of the 3-phenylthio-dihydropyridinone derivative (**4**) was carried out under the influence of a proper Lewis acid catalyst. Here again, selection of a suitable electron-withdrawing *N*-protecting group was an important factor, which could well be understood by its effect in lowering the LUMO of the dienophile by the MO calculation.

Table II MO Calculation for the Dienophiles

			
Dienophile	Experimental results	Calculation	
		HOMO	LUMO
	(not tried)	-8.7129	-0.3121
	EtAlCl ₂ (2 eq.) toluene, room temperature, 2 h no reaction	-8.7104	-0.454
	EtAlCl ₂ (2 eq.) toluene, 0 °C, 1 h N-deprotection	-8.9434	-0.4767
	EtAlCl ₂ (2 eq.) toluene, room temperature, 15 min 80%	-8.8990	-0.5665
	EtAlCl ₂ (2 eq.) toluene, room temperature, 2 h 77%	-8.9347	-0.5797
	ZnBr ₂ (1 eq.) CH ₂ Cl ₂ , room temperature, 24 h 83%	-8.6847	-0.8743

EXPERIMENTAL

Melting points are uncorrected. Unless otherwise noted, ir spectra were measured as a KBr disk, and ^1H -nmr spectra were measured as a solution in CDCl_3 .

3,3-Bis(phenylthio)-2-piperidone (11) *N*-Trimethylsilyl-2-piperidone (**10**) A mixture of 2-piperidone (30.0 g, 0.30 mmol) and hexamethyldisilazane (64 ml, 0.30 mmol) was heated at 140 °C for 14 h under Ar atmosphere. After cooling to room temperature, the mixture was carefully distilled at atmospheric pressure to remove excess silylamine (110–130 °C). The residue was then subjected to a second distillation under reduced pressure (14 mmHg) to afford the desired *N*-TMS-piperidone (**10**, 15 g, bp 80–90 °C, 40%) as a colorless oil. Redistillation of this fraction gave a higher purity: bp 72–74 °C (10 mmHg)³; ir 3340, 2950, 1670, 1630 cm^{-1} ; ^1H nmr (60 MHz) δ 0.55 (9H, s), 1.60–1.95 (4H, m), 2.20–2.50 (2H, m), 3.10–3.40 (2H, m).

3,3-Bis(phenylthio)-2-piperidone (11) To a cooled (–78 °C) and stirred solution of the *N*-TMS-piperidone (**10**, 14.66 g, 85.57 mmol) and diphenyl disulfide (41.10 g, 188.25 mmol) in dry THF (300 ml) was added $\text{KN}(\text{TMS})_2$ (0.5M toluene solution, 377 ml, 188.25 mmol) and the mixture was kept stirring at room temperature for 30 min. The mixture was quenched by the addition of sat aq. NH_4Cl (100 ml) and extracted with CH_2Cl_2 (500 ml x 2). The organic layer was washed with sat aq. NaCl (500 ml) and dried over Na_2SO_4 . Evaporation of the solvent gave a residue, which was purified by column chromatography (SiO_2 , 280 g, n-hexane/ CH_2Cl_2 =1/1) to afford the pure lactam (**11**, 20.08 g, 74.4%) along with 3-phenylthio-2-piperidone (0.21 g, 1.2%). **11**: colorless prism; mp 156.0–156.5 °C (AcOEt); ir 3350, 3225, 3075, 2950, 1670 cm^{-1} ; ^1H nmr (500 MHz) δ 1.72–1.90 (2H, m), 1.97 (2H, t, J =6.2 Hz), 3.18 (2H, dt, J =2.4, 6.0 Hz), 6.55 (1H, br s), 7.32–7.41 (6H, m), 7.65–7.68 (4H, m); LREIms m/z (%): 315 (M^+ , 4.1), 178 (100). Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{NOS}_2$: C, 64.73; H, 5.43; N, 4.44; Found: C, 64.80; H, 5.32; N, 4.47.

***N*-Benzenesulfonyl-3,3-bis(phenylthio)-2-piperidone (12a)** To a cooled (–78 °C) and stirred solution of **11** (1.00 g, 3.17 mmol) in dry THF (30 ml) was added *n*-BuLi (2.2 ml, 3.60 mmol) and the resulting mixture was kept stirring at this temperature for 15 min. Next was added benzenesulfonyl chloride

(0.41 ml, 3.21 mmol) and the mixture was kept stirring at room temperature for 1 h. The mixture was then quenched by the addition of sat aq. NH_4Cl (10 ml) and extracted with CH_2Cl_2 (30 ml x 3). The organic layer was washed with brine (20 ml) and dried over Na_2SO_4 . Evaporation of the solvent gave a residue, which was purified by column chromatography (SiO_2 , 30 g, n-hexane/ AcOEt = 3/1) to afford **12a** (1.39 g, 96.4%): colorless prism; mp 155.5-156.0 °C (MeOH); ir 3150, 1690 cm^{-1} ; ^1H nmr (500 MHz) δ 2.02-2.04 (4H, m), 3.86-3.89 (2H, m), 7.24-7.26 (4H, m), 7.32-7.38 (6H, m), 7.53-7.58 (2H, m), 7.66-7.71 (1H, m), 8.03-8.06 (2H, m); LREIms m/z (%): 455 (M^+ , 2.4), 346 (100). *Anal.* Calcd for $\text{C}_{23}\text{H}_{21}\text{NO}_3\text{S}_3$: C, 60.63; H, 4.65; N, 3.07; Found: C, 60.54; H, 4.49; N, 3.10.

3-Phenylthio-5,6-dihydro-2(1H)-pyridinone (13) To a cooled (0 °C) and stirred solution of **11** (2.76 g, 8.75 mmol) in CH_2Cl_2 (200 ml) was added a cooled (0 °C) solution of mCPBA (2.26 g, 80 %, 10.05 mmol) in CH_2Cl_2 (10 ml), and then sat aq. NaHCO_3 (1 ml). After stirring for 15 min with cooling, the mixture was quenched by the addition of sat aq. NaHCO_3 (80 ml). The organic layer was further washed with brine (80 ml) and dried over Na_2SO_4 . Evaporation of the solvent gave a residue, which was taken into benzene (30 ml) and heated under reflux for 30 min. Concentration of the mixture under reduced pressure and purification of the residue by column chromatography (SiO_2 , 36 g, n-hexane / AcOEt = 2 / 1) gave **13** (1.62 g, 89.75%) as a powder : mp 112-114 °C ; ir 3300, 3090, 3000, 2950, 2895, 1680, 1640 cm^{-1} ; ^1H nmr (500 MHz) δ 2.34 (2H, dt, $J=4.6, 7.1$ Hz), 3.42 (2H, dt, $J=2.8, 7.1$ Hz), 6.00 (1H, t, $J= 4.6$ Hz) 6.38 (1H, br s), 7.32-7.40 (3H, m), 7.47-7.50 (2H, m); LREIms m/z (%): 205 (M^+ , 100). HRFABms Calcd for $\text{C}_{11}\text{H}_{12}\text{NOS}$ (MH^+): 206.0640 ; Found: 206.0644.

***N*-Benzenesulfonyl-3-phenylthio-5,6-dihydro-2(1H)-pyridinone (4a)**

1) Path A: from N-benzenesulfonyl lactam (12a) To a cooled (0 °C) and stirred solution of **12a** (1.92 g, 4.21 mmol) in CH_2Cl_2 (200 ml) was added a cooled (0 °C) solution of mCPBA (1.09 g, 5.06 mmol) in CH_2Cl_2 (10 ml) and then sat aq. NaHCO_3 (1 ml). After stirring for 15 min under cooling, the mixture was quenched by the addition of sat aq. NaHCO_3 (50 ml). The organic layer was further washed with brine (50 ml) and dried over Na_2SO_4 . Evaporation of the solvent gave a residue, which was taken into benzene (30

ml) and heated under reflux for 30 min. Concentration of the mixture under reduced pressure and purification by column chromatography (SiO_2 , 44 g, n-hexane / AcOEt = 7 / 3) gave **4a** (1.20 g, 82.49%) as a colorless powder : mp 119 °C (MeOH); ir 1670, 1610 cm^{-1} ; ^1H nmr (500 MHz) δ 2.50 (2H, dt, $J=4.7, 6.6$ Hz), 4.06 (2H, t, $J=6.6$ Hz), 6.08 (1H, t, $J=4.7$ Hz) 7.33-7.42 (5H, m), 7.51-7.56 (2H, m), 7.61-7.65 (1H, m), 8.05-8.08 (2H, m); LREIMS m/z (%): 345 (M^+ , 90.9), 109 (100). Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2\text{S}_2$: C, 61.98; H, 4.59; N, 4.25; Found: C, 58.79; H, 4.19; N, 4.06.

2) Path B: from NH-dihydropyridinone (13) To a stirred solution of **13** (100 mg, 0.49 mmol) in THF (5 ml) was added a LDA solution [prepared from diisopropylamine (0.09 ml, 0.58 mmol) and n-BuLi (0.58 mmol) in THF (5 ml)] at -78 °C, and the mixture was kept stirring for 10 min at this temperature. Next was added PhSO_2Cl (0.07 ml, 0.58 mmol) and the resulting mixture was stirred at room temperature for 30 min. The mixture was quenched by the addition of sat aq. NH_4Cl (5 ml) and extracted with CH_2Cl_2 (50 ml). The organic layer was washed with sat aq. NH_4Cl (15 ml) and brine (15 ml), and dried over Na_2SO_4 . Evaporation of the solvent under reduced pressure gave a residue, which was purified by column chromatography (SiO_2 , 23 g, n-hexane / AcOEt = 7 : 3) to afford **4a** (160 mg, 94.0%).

N-Methoxycarbonyl-3,3-bis(phenylthio)-2-piperidone (12b) To a cooled (-78 °C) and stirred solution of **11** (1.00 g, 3.17 mmol) in dry THF (30 ml) was added n-BuLi (2.2 ml, 3.49 mmol) and the resulting mixture was kept stirring at this temperature for 15 min. To it was next added methyl chloroformate (0.3 ml, 3.49 mmol) and the mixture was kept stirring at room temperature for 1 h. The mixture was then quenched by the addition of sat aq. NH_4Cl (5 ml) and extracted with CH_2Cl_2 (200 ml). The organic layer was washed with sat aq. NH_4Cl (40 ml) and brine (40 ml) and dried over Na_2SO_4 . Evaporation of the solvent gave a residue, which was purified by column chromatography (SiO_2 , 17 g, n-hexane/ AcOEt = 10 / 3) to afford **12b** (1.1g, 94.0 %) as a colorless solid: mp 110-111 °C; ir 2940, 1750, 1660 cm^{-1} ; ^1H nmr (500 MHz) δ 1.91-1.96 (2H, m), 2.08-2.11 (2H, m), 3.69 (2H, t, $J=6.1$ Hz) 3.84 (3H, s), 7.35-7.37 (2H, m), 7.39-7.43 (1H, m), 7.65-7.68 (2H, m); LREIMS m/z (%): 373 (M^+ , 5.5), 236 (100). HRFABms Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_3\text{S}_2$ (MH^+): 374.0885; Found: 374.0891.

***N*-Methoxycarbonyl-3-phenylthio-5,6-dihydro-2(1*H*)-pyridinone (4b)** To a cooled (0 °C) and stirred solution of **12b** (234 mg, 0.63 mmol) in CH₂Cl₂ (60 ml) was added a cooled (0 °C) solution of mCPBA (149 mg, 0.69 mmol) in CH₂Cl₂ (15 ml) and then sat aq. NaHCO₃ (1 ml). After being stirred for 15 min under cooling, the mixture was quenched by the addition of sat aq. NaHCO₃ (20 ml). The organic layer was further washed with brine (30 ml) and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was taken into benzene (10 ml) and heated under reflux for 30 min. Concentration of the mixture under reduced pressure and purification of the residue by column chromatography (SiO₂, 17 g, n-hexane / AcOEt = 10 / 3) gave **4b** (160 mg, 98.0%). **4b**: mp 77-78 °C (AcOEt / n-hexane): Ir 3050, 3000, 2950, 2850, 1760, 1710, 1600 cm⁻¹; ¹H nmr (500 MHz) δ 2.40 (2H, dt, *J*=6.4, 9.4 Hz), 3.89 (3H, s), 3.94 (2H, t, *J*=6.4 Hz), 6.18 (1H, t, *J*=4.9 Hz) 7.18 (2H, t like), 7.36-7.40 (3H, m); LREIms *m/z* (%): 263 (M⁺, 100), HRFABms Calcd for C₁₃H₁₄NO₃S: 264.0695; Found: 264.0696. *Anal.* Calcd for C₁₃H₁₃NO₃S: C, 59.30; H, 4.98; N, 5.32; Found: C, 59.17; H, 4.90; N, 5.30.

***N*-Allyloxycarbonyl-3,3-bis(phenylthio)-2-piperidone (12c)** To a cooled (-78 °C) and stirred solution of **11** (100 mg, 0.31 mmol) in THF (10 ml) was added *n*-BuLi (0.36 mmol) and the mixture was kept stirring at this temperature for 15 min. Next was added allyloxycarbonyl chloride (0.36 ml, 0.39 mmol). After being stirred at this temperature for 5 min, the mixture was quenched by the addition of sat aq. NH₄Cl and extracted with CH₂Cl₂ (20 ml x 3). The combined organic layer was washed with brine (20 ml) and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was purified by SiO₂ column chromatography (5 g, n-hexane / AcOEt = 10 / 1) to afford **12c** (112.0 mg, 88.5%) as a yellow oil: Ir (neat) 3050, 2950, 1760, 1710, 1640 cm⁻¹; ¹H nmr (500 MHz) δ 1.95 (2H, dt, *J*=6.1, 12.1 Hz), 2.10 (2H, t, *J*=5.6 Hz) 3.70 (2H, t, *J*=6.1 Hz), 4.73 (2H, dt, *J*=1.5, 5.7 Hz), 5.29 (1H, ddd, *J*=1.5, 2.7, 11.5 Hz), 5.43 (1H, ddd, *J*=1.5, 3.0, 17.0 Hz), 5.96 (1H, m), 7.36 (4H, m), 7.40 (2H, m), 7.76 (4H, m); LREIms *m/z* (%): 399 (M⁺, 0.8), 290 (100).

***N*-Allyloxycarbonyl-3-phenylthio-5,6-dihydro-2(1*H*)-pyridinone (4c)**

1) Path A : from N-allyloxycarbonyl lactam (12c) To a cooled (0 °C) and stirred solution of **12c** (5.63 g, 14.11 mmol) in CH₂Cl₂ (250 ml) was added mCPBA (3.1 g, 14.37 mmol) portionwise. After stirring for 5 min, the mixture was diluted with CH₂Cl₂ (100 ml) and sat aq. NaHCO₃ (100 ml). The organic layer was separated and the aqueous layer was re-extracted by CH₂Cl₂ (100 ml x 2). The combined organic layer was washed with brine (100 ml) and dried over Na₂SO₄. Evaporation of the solvent gave a residue (6.18 g), which was taken into benzene (100 ml) and heated under reflux for 5 min. The mixture was then cooled to room temperature and concentrated to afford a residue, which was purified by SiO₂ column chromatography (200 g, AcOEt / n-hexane = 1 / 9), furnishing the desired *N*-allyloxycarbonyl dienophile (**4c**, 3.23 g, 79.2%): Ir 3050, 2925, 1760, 1710, 1640, 1615 cm⁻¹; ¹H nmr (500 MHz) δ 2.39 (2H, dt, *J*=4.7, 6.3 Hz), 3.94 (2H, t, *J*=6.3 Hz), 4.77 (2H, dt, *J*=1.4, 5.5 Hz), 5.28 (1H, dt, *J*=1.4, 11.5 Hz), 5.45 (1H, ddd, *J*=1.4, 3.0, 16.1 Hz), 5.79 (1H, m), 6.15 (1H, t, *J*=4.7 Hz), 7.37 (2H, m), 7.47 (1H, m), 7.49 (2H, m); LREIMS *m/z* (%): 289 (M⁺, 63.9), 204 (59).

2) Path B: from NH-dihydropyridinone (13) By the same procedure as for **4a**, NH-dihydropyridinone (**13**, 1.25 g, 6.10 mmol) in THF (20 ml) was treated with LDA (6.40 mmol) at -78 °C, followed by the addition of allyloxycarbonyl chloride (0.68 ml, 6.40 mmol) to afford, after usual work-up and purification, the *N*-allyloxycarbonyl dienophile (**4c**, 1.45 g, 82.5%).

***N*-*t*-Butoxycarbonyl-3,3-bis(phenylthio)-2-piperidone (12d)** To a stirred solution of **11** (0.5 g, 1.58 mmol) in CH₂Cl₂ (20 ml) was added a solution of DMAP (0.29 g, 2.37 mmol) in CH₂Cl₂ (3 ml) at room temperature. The mixture was kept stirring, while a solution of (BOC)₂O (1.03 g, 4.74 mmol) in CH₂Cl₂ (5 ml) was added by syringe, which was followed by the addition of Et₃N (0.33 ml, 2.47 mmol). After being stirred for 3.5 h at room temperature, the mixture was quenched by the addition of H₂O (10 ml) and CH₂Cl₂ (100 ml). The organic layer was separated, further washed with brine (50 ml) and dried over MgSO₄. Evaporation of the solvent gave a residue (0.95 g), which was purified by column chromatography (SiO₂, 20 g, n-hexane / AcOEt = 1 / 7) to give **12d** (0.65 g, 99%) as a white solid mass: mp 115-116 °C (AcOEt / n-hexane); ir 3050, 2950, 2850, 1710, 1610 cm⁻¹; ¹H nmr (500 MHz) δ 1.53 (9H, s), 1.94, (2H,

m), 2.05 (2H, m), 3.60 (2H, t, $J=6.1$ Hz), 7.33-7.42 (6H, m), 7.68 (4H, m); LRFABms m/z (%): 416 (MH^+ , 14.4), 360 (68.3); HRFABms Calcd for $C_{22}H_{26}NO_3S_2$ (MH^+): 416.1354; Found: 416.1358.

***N*-*t*-Butoxycarbonyl-3-phenylthio-5,6-dihydro-2-(1*H*)-pyridinone (4d)**

1) *Path A: from N-t-butoxycarbonyl derivative (12d)* To a cooled ($0^\circ C$) and stirred mixture of **12d** (2.20 g, 5.3 mmol) in CH_2Cl_2 (80 ml) and sat aq. $NaHCO_3$ (30 ml) was added slowly a CH_2Cl_2 (20 ml) solution of mCPBA (1.25 g, 80%, 5.83 mmol) over 30 min under ice-cooling. After being stirred at this temperature for 1 h, the mixture was diluted with AcOEt (200 ml) and sat aq. $NaHCO_3$ (30 ml). The organic layer was separated and washed with brine and dried over $MgSO_4$. Concentration of the solvent gave a residue (2.62 g), which was taken into benzene (50 ml) and heated under reflux for 1 h. After being cooled to room temperature, the mixture was diluted with AcOEt and sat aq. $NaHCO_3$. The organic layer was separated and washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give a residue (2.53 g). Purification by column chromatography (SiO_2 , 120 g, AcOEt / n-hexane = 1 / 5) gave **4d** (1.38 g, 94%) as a colorless crystal: mp $111-112^\circ C$ (AcOEt / n-hexane); ir 3050, 2975, 2825, 1760, 1710, 1690, 1610 cm^{-1} ; 1H nmr (500 MHz) δ 1.54 (9H, s), 2.35, (2H, m), 3.84 (2H, t, $J=6.1$ Hz), 6.07 (1H, t like), 7.34-7.40 (3H, m), 7.47-7.48 (2H, m); LRFABms m/z (%): 305 (MH^+ , 38.2); HRFABms Calcd for $C_{16}H_{20}NO_3S$ (MH^+): 305.1086; Found: 305.1078.

2) *Path B: from NH-dihydropyridinone (13)* To a stirred solution of **13** (0.5 g, 2.43 mmol) in CH_2Cl_2 (20 ml) was added a solution of DMAP (0.59 g, 4.86 mmol) in CH_2Cl_2 (3 ml) at room temperature. The mixture was kept stirring, while a solution of $(BOC)_2O$ (2.12 g, 9.72 mmol) in CH_2Cl_2 (5 ml) was added by syringe, which was followed by the addition of Et_3N (0.66 ml, 4.86 mmol). After being stirred at room temperature overnight, the mixture was quenched by the addition of H_2O (10 ml) and CH_2Cl_2 (100 ml). The organic layer was separated, further washed with brine (50 ml) and dried over $MgSO_4$. Evaporation of the solvent gave a residue (4.27 g), which was purified by column chromatography (SiO_2 , 20 g, n-hexane / AcOEt = 1 / 5) to give the *N*-BOC dienophile (**4d**, 2.04 g, 92.6%) as a white solid mass.

Diels-Alder Reaction of the *N*-Benzenesulfonyl Dienophile (4a) To a cooled and stirred suspension of ZnBr_2 (782.3 mg, 3.47 mmol) in dry CH_2Cl_2 (10 ml) was added **4a** (1.00 g, 2.89 mmol) in CH_2Cl_2 (20 ml) by a canula, followed by the immediate addition of 2-trimethylsilyloxybutadiene (**5**, 2.00 ml, ~20.0 mmol) at 0 °C. The mixture was warmed to room temperature and kept stirring for 24 h. It was then quenched by the addition of sat aq. NaHCO_3 (5 ml) and CH_2Cl_2 (30 ml). The organic layer was separated and washed with brine (5 ml). The entire aqueous layer was re-extracted with CH_2Cl_2 (10 ml x 2). The combined organic layer was dried over Na_2SO_4 and concentrated to give a residue (2.59 g), which was then taken into MeOH (20 ml) and treated with 10% citric acid (5 ml) at room temperature. After being stirred for 20 min, the mixture was concentrated under reduced pressure. The residue was then diluted with CH_2Cl_2 (70 ml) and washed with brine (10 ml). The aqueous layer was re-extracted with CH_2Cl_2 (20 ml x 2). The combined organic layer was dried over Na_2SO_4 and concentrated to afford a residue (1.19 g). Purification by SiO_2 column chromatography (40 g, AcOEt / *n*-hexane = 1/2) afforded the desired fraction (1.13 g) along with recovered starting material (**4a**, 60.0 mg, 6.0 %). The desired fraction was further recrystallized from AcOEt to afford the pure material (**6**, $\text{P}=\text{SO}_2\text{Ph}$, 998.6 mg, 83.3%) as a colorless crystal: mp 177.0-178.0 °C (AcOEt); ir 3075, 2975, 1710, 1685 cm^{-1} ; ^1H nmr (500 MHz) δ 1.67 (1H, td, $J=5.5$, 7.3 Hz), 1.82 (1H, m), 2.10-2.19 (2H, m), 2.25-2.29 (1H, m), 2.39-2.53 (4H, m), 4.09-4.16 (1H, m), 4.19-4.25 (1H, m), 6.97-7.00 (2H, m), 7.13-7.18 (2H, m), 7.31-7.36 (1H, m), 7.56-7.61 (2H, m), 7.68-7.72 (1H, m), 8.08-8.11 (2H, m); LREIMS m/z (%): 415 (M^+ , 6.1), 306 (4), 77 (100). Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_4\text{S}_2$: C, 60.70; H, 5.09; N, 3.37; Found: C, 60.54; H, 5.01; N, 3.27.

Diels-Alder Reaction of the *N*-Methoxycarbonyl Dienophile (4b) To a cooled (-20 °C) and stirred solution of EtAlCl_2 (0.5 ml, 0.5 mmol) in CH_2Cl_2 (5 ml) was added a cooled mixture of **4b** (263 mg, 1 mmol) and 2-trimethylsilyloxybutadiene (**5**, 2 mmol) in CH_2Cl_2 (5 ml) by a canula. The mixture was kept stirring at this temperature for 15 min and warmed to 0 °C. Then a further amount of EtAlCl_2 (1.5 mmol in toluene 2 ml) was injected to this mixture dropwise and the resulting mixture was kept stirring at 0 °C for 1 h and at room temperature for 0.5 h. The mixture was then quenched by the addition of 5% HCl (10 ml) and THF (10 ml). After being stirred at room temperature for several hours, the mixture was extracted with

CH₂Cl₂ (50 ml). The organic layer was separated, washed with brine (10 ml x 2) and dried over MgSO₄. Concentration of the dried solvent afforded a residue, which was purified by SiO₂ column chromatography (AcOEt / n-hexane = 1/1) to afford **6** (P=CO₂Me, 150 mg, 45.0%) as a colorless prism, along with the *N*-deprotected compound (**6**, P=H, 88 mg, 32.0%). **6** (P=CO₂Me): mp 129~130 °C (AcOEt / n-hexane); ir 3050, 2950, 2920, 1710, 1700, 1600 cm⁻¹; ¹H nmr (500 MHz) δ 1.58 (1H, m), 1.92 (1H, m), 2.29-2.40 (4H, m), 2.46-2.55 (3H, m), 3.90 (1H, m), 3.91 (3H, s), 4.03 (1H, m), 7.33-7.43 (3H, m), 7.45-7.47 (2H, m); LRFABms *m/z* (%): 334 (MH⁺, 100); *Anal.* Calcd for C₁₇H₁₉NO₄S: C, 61.24; H, 5.74; N, 4.20; Found: C, 61.16; H, 5.73; N, 4.08. **6** (P=H): Ir 3350, 3050, 2950, 1710, 1660 cm⁻¹; ¹H nmr (500 MHz) δ 1.65 (1H, m), 2.00 (1H, m), 2.33-2.43 (3H, m), 2.45-2.55 (3H, m), 2.66 (1H, m), 3.40 (2H, m), 6.10 (1H, br s), 7.32-7.42 (3H, m), 7.55-7.57 (2H, m); LREIms *m/z* (%): 275 (M⁺, 8.74), 166 (32); HRFABms Calcd for C₁₅H₁₈NO₂S (MH⁺): 276.1058; Found: 276.1057.

Besides these cycloadducts, starting dienophile (**4b**, 39 mg) and its *N*-deprotected derivative (**13**, 10 mg) were recovered.

Diels-Alder Reaction of the *N*-Allyloxycarbonyl Dienophile (4c**)** To a cooled (0 °C) and stirred solution of **4c** (1.32 g, 4.56 mmol) in dry toluene (50 ml) was added EtAlCl₂ (9.2 ml, 9.20 mmol) and afterwards 2-TMS-butadiene (**5**, 4.0 ml, 40.0 mmol) was injected immediately. The mixture was warmed to room temperature and stirred for 15 min. The mixture was quenched by the addition of 5% HCl (10 ml) and MeOH (20 ml). The resulting mixture was kept stirring for 30 min. Then the organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (200 ml x 3). The combined organic layer was washed with brine (100 ml) and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was purified by SiO₂ column chromatography (SiO₂, 150 g, AcOEt / n-hexane = 1/10) to afford, from the first fraction, the dimethyl ketal of the *N*-allyloxycarbonylisoquinolone (153.4 mg, 8.3%), which could be deketalized (acetone-H₂O-amberlite) and characterized as *N*-allyloxycarbonylisoquinolone (**6**, P=CO₂CH=CH₂). From the second fraction, *N*-allyloxycarbonylisoquinolone (**6**, P=CO₂CH=CH₂, 331.1 mg, 20.2%) was obtained as a colorless oil. From the third and more polar fraction, the deprotected dimethylketal of *NH*-isoquinolone (**6**, P=H, 180.0 mg, 12.3%) was obtained and characterized as *NH*-

isoquinolone (6, P=H). From the most polar fraction the *NH*-isoquinolone (6, P=H, 492 mg, 38.7%) was obtained.

6 (P=CO₂CH=CH₂): Ir 3050, 2910, 2850, 1760, 1710, 1640 cm⁻¹; ¹H nmr (500 MHz) δ 1.58 (1H, m), 1.92 (1H, m), 2.28-2.39 (3H, m), 2.39-2.44 (1H, m), 2.45-2.56 (3H, m), 3.90 (1H, ddd, *J*=4.4, 7.7, 12.6 Hz), 4.04 (1H, ddd, *J*=4.6, 7.4, 12.6 Hz), 4.79-4.81 (1H, m), 5.32 (1H, ddd, *J*=2.5, 5.1, 10.5 Hz), 5.47 (1H, ddd, *J*=1.4, 3.0, 18.7 Hz), 6.00 (1H, m), 7.31-7.35 (2H, m), 7.40-7.44 (1H, m), 7.46 (2H, m); LREIMS *m/z* (%): 359 (M⁺, 26.6), 149 (100).

Computational Methods

The starting conformation of 2(*1H*)-dihydropyridinone was constructed by SYBYL⁶ program using standard bond length and bond angles. The conformation was minimized by the semiempirical calculations program PM3 in MOPAC⁵ which run on Digital Equipment micro VAX-4000/200. Other starting conformations were constructed by adding substitution groups and scanning its torsional angles. These conformations were subjected to PM3 calculation with full geometrical optimization.

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