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New Building Blocks, 3,5-Dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-Dioxides; Preparation and their Diels-Alder Reaction with Dimethyl Acetylenedicarboxylate

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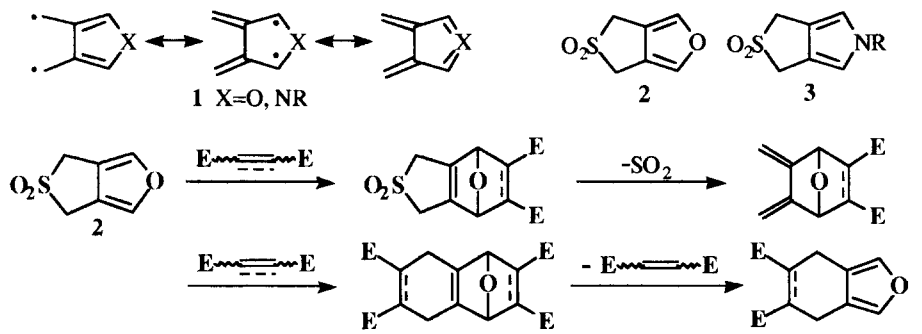
Abstract: New building blocks, 3,5-dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxides **3**, have been prepared by the oxidation of their corresponding pyrroline derivatives **4** with DDQ or Chemical MnO_2. The Diels-Alder reaction of **3** with dimethyl acetylenedicarboxylate gave new types of compounds: 7-aza-2,3-dimethylenenorbornenes **A**, the 1:2 adducts **B**, 1a,3a,6,9-tetrahydrobenz[*g*]indoles **C**, and dihydroindolosulfolene **D** depending on the reaction conditions and the *N*-substituents. The reaction of **3** with bis(*tert*-butylsulfonyl)acetylene was also described.

3,4-Dimethylenefuran and 3,4-dimethylenepyrroles **1** are π-conjugated non-Kekulé molecules and have aroused theoretical[2] and synthetic interest. They were generated from the corresponding diazenes[3] or postulated as transient intermediates in base-catalized rearrangement of the bis-allenyl compounds.[4] Unfortunately neither starting material is stable and allows functionalization. Since 3-sulfolenes are known to be excellent precursors to the corresponding dienes, heteroaromatic-fused 3-sulfolenes at 3,4-position seemed to be ideal precursors to 3,4-dimethylenefuran and pyrroles. We have already reported the preparation of the furan-fused sulfolene **2** and its synthetic applications.[5-8] Although we could not get any evidence of the generation of 3,4-dimethylenefuran from **2**, the furan-fused sulfolene **2** turned out to be a useful building block. Since both furan and 3-sulfolene moieties can be used as the diene component in Diels-Alder reaction, **2** could sequentially react with two types of dienophiles (first on the furan moiety and then on the diene moiety resulting from cheletropic desulfonylation) and offer a rapid elaboration of multicyclic systems (Scheme 1).

In this context, a series of pyrrole-fused 3-sulfolenes, 3,5-dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxides **3** containing a variety of *N*-substituents are promising synthetic building blocks. In a preliminary paper,[9] we



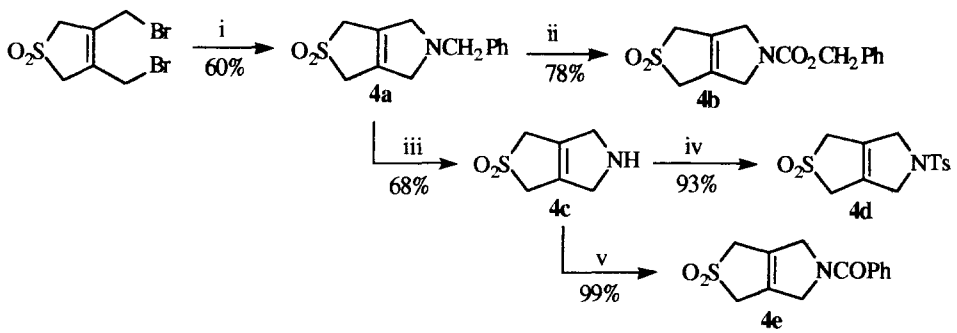
Scheme 1

have reported the efficient and general methods for preparation of **3** and their Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAD) to give new types of compounds : 7-aza-2,3-dimethylenenorbornenes **A**, the 1:2 adducts **B**, 1a,3a,6,9-tetrahydrobenz[*g*]indoles **C**, and dihydroindolosulfolene **D** depending on the reaction conditions and the *N*-substituents. Since these types of compounds are synthetically interesting especially for multifunctional multicyclic compounds such as alkaloids and potent tumor promoters, teleocidins,[10] we would like to describe the full details of both the preparations of **3** and their Diels-Alder reaction with DMAD.

PREPARATION OF 3,5-DIHYDRO-1H-THIENO[3,4-c]PYRROLE 2,2-DIOXIDES

Our synthetic plan relied on the preparation of the corresponding pyrrolinesulfolenes and the following oxidation of them. For this purpose, the pyrrolinesulfolenes **4** were prepared as shown in Scheme 2. The derivatives **4a** and **4b** were prepared from 3,4-bis(bromomethyl)-2,5-dihydrothiophene 1,1-dioxide, which is easily obtained by brominating the cycloadduct of 2,3-dimethylbuta-1,3-diene and sulfur dioxide, by a modification of the literature method.[11] Cleavage of the benzyloxycarbonyl group of **4b** was attempted by the literature procedure (15% HBr in glacial acetic acid), but the best yield was only 17% in our hands (lit.[11] 64%). This low yielding cleavage was improved by using Olofson's *N*-dealkylation reaction of tertiary amines.[12] When the *N*-benzylpyrroline **4a** was treated with α-chloroethyl chloroformate in $ClCH_2CH_2Cl$, the chloroethyl carbamate was obtained in 96% yield. This carbamate was warmed to 50 °C in MeOH for 30 min to give **4c** (R=H) in 71% yield. *N*-(*p*-Tolylsulfonyl)- and *N*-benzoyl-pyrrolines **4d** and **4e** were prepared by treating **4c** with the corresponding chlorides in the presence of bases in high yields.

Next, we set about oxidation of the pyrrolinesulfolenes **4** to the corresponding pyrrolsulfolenes **3**[13] (Table 1). The *N*-benzylpyrrolinesulfolene **4a** was converted into the pyrrole **3a** in 100% yield by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane, but the reaction of **4c** (R=H) with DDQ was rather intractable and gave only a 40% yield of **3c** at best. Further, the reactions of **4b**, **4d** and **4e**, which have electron-withdrawing substituents on the nitrogen, with DDQ did not give any pyrrolesulfolenes **3**. Oxidation of **4b**, **4d** and **4e** was attempted by using NiO_2,[14] $(NH_4)_2Ce(NO_3)_6$[9] and active MnO_2.[15] Only active MnO_2 effected the desired transformation, giving low yields of the pyrrolesulfolenes **3**. Shioiri *et al.* reported the superiority of 'chemical manganese dioxide' (CMD) over the usually available activated manganese dioxide (Aldrich) on oxidation of thiazolidines to thiazoles .[16] Several kinds of CMDs are industrially produced for batteries and readily available. When the *N*-benzyloxycarbonylpyrrolinesulfolene **4b** was treated with CMD-



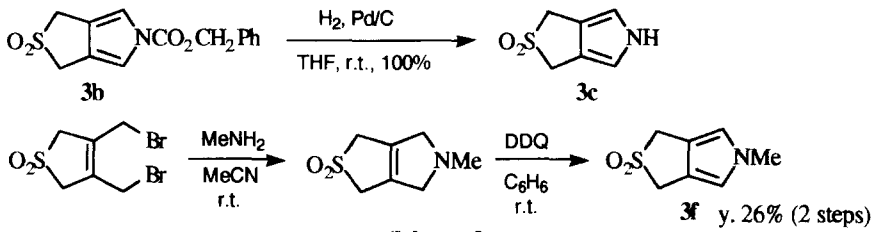
Scheme 2 *Reagents and conditions* : i, $PhCH_2NH_2$, MeCN; ii, $ClCO_2CH_2Ph$, C_6H_6; iii, $ClCO_2CHClMe$, $ClCH_2CH_2Cl$ then MeOH, 50 °C; iv, *p*-$MeC_6H_4SO_2Cl$, pyridine ; v, PhCOCl, K_2CO_3, $CHCl_3$.

Table 1. Oxidation of pyrrolinesulfolenes **4** to pyrrolesulfolenes **3**

a R= CH_2Ph
b CO_2CH_2Ph
c H
d Ts
e COPh

Entry	R		Reagent	Conditions	Yield of **3** (%)	Recovered **4** (%)
1	CH_2Ph	**4a**	DDQ	Dioxane, r.t., 3 h	100	0
2	H	**4c**	DDQ	benzene, 5 °C, 15 min	40	0
3	CO_2CH_2Ph	**4b**	CMD*	benzene, r.t., 4 days	59	31
4			CMD	benzene, r.t., 14 days	69	0
5	Ts	**4d**	CMD	CH_2Cl_2, r.t., 5 days	50	22
6	COPh	**4e**	CMD	benzene, r.t., 4 days	54	41

* 'Chemical MnO_2' (CMD-U)



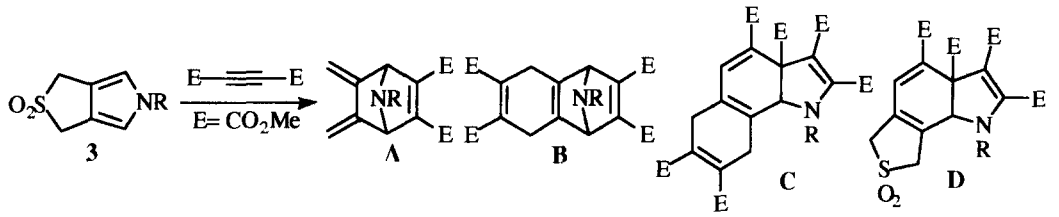
Scheme 3

U[17] (30 equiv) in benzene at room temperature for 4 days, the pyrrolesulfolene **3b** was obtained in 59% yield (86% based on consumed **4b**). Continuing the reaction for 2 weeks gave a slightly improved yield of **3b** (69%) with no recovery of **4b**. The former procedure was applied to compounds **4d** and **4e** to give **3d** and **3e**, respectively, in good yields together with some starting materials. Although the reaction does not go to completion, both the reaction operation and the separation of **3** and **4** are easy and the starting material can be recycled. The *N*-benzyloxycarbonylpyrrole **3b** thus obtained was deprotected to give **3c** (R=H) in a quantitative yield (Scheme 3). The *N*-methylpyrrole **3f** was prepared from the reaction of 2,3-bis(bromomethyl)buta-1,3-diene and methylamine followed by DDQ oxidation.

DIELS-ALDER REACTION OF THE PYRROLESULFOLENES WITH DMAD

Diels-Alder reactions of the pyrrole-fused sulfolenes **3** with dimethyl acetylenedicarboxylate (DMAD) were studied, and the results are summarized in Table 2. Heating the pyrrolesulfolene **3a** (R=CH_2Ph) with 3 equivalents of DMAD in benzene at 100 °C in a sealed tube for 4 h afforded 7-aza-2,3-dimethylenenorbornene **A** (R=CH_2Ph) and 1a,3a,6,9-tetrahydrobenz[*g*]indole **C** (R=CH_2Ph) in 28 and 47% yields, respectively, along with the starting pyrrole (15%) (Entry 1). All attempts to get **A** selectively by decreasing the quantity of DMAD and/or lowering the reaction temperature were unsuccessful. For example, when **3a** was heated with 1.0 equiv. of DMAD at 90 °C for 26 h, the ratio of **A** to **C** was 1:2.4. Reaction of 4 equiv. of DMAD with **3a** at 140 °C for 16 h gave **C** in 97% yield. Compound **C** was also obtained at 4 kbar. At 12 kbar, the dihydroindolosulfolene **D** was obtained. The reaction of the *N*-methylpyrrolesulfolene **3f** with DMAD (3 equiv.) gave **C** (R=Me)

Table 2. Diels-Alder reaction of a series of 3,5-dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxides with DMAD



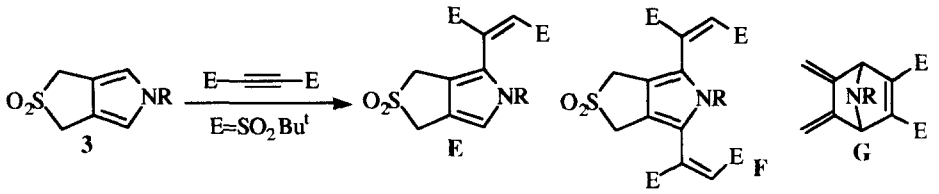
Entry	R		DMAD (eq)	Solvent	Temp. (°C)	Pressure (kbar)	Time (h)	Yield A	B	C	D	3
1	CH_2Ph	**3a**	3	benzene	100		4	28		47		15
2	CH_2Ph	**3a**	4	benzene	140		16			97		
3	CH_2Ph	**3a**	3	CH_2Cl_2	r.t.	4	48			62		
4	CH_2Ph	**3a**	3	CH_2Cl_2	r.t.	12	48			2	38	
5	Me	**3f**	3	benzene	150		3			73		
6	CO_2CH_2Ph	**3b**	3	benzene	150		13		85			
7	CO_2CH_2Ph	**3b**	3	CH_2Cl_2	r.t.	12	48		52			16
8	Ts	**3d**	3	benzene	170		14		97			
9	COPh	**3e**	3	benzene	170		8		99			

in 73% yield. Compounds **3b**, **3d**, and **3e**, which have electron-withdrawing substituents on the nitrogen, react with DMAD to give only the 1:2 adducts **B** in high yields (Entry 6-9). The parent pyrrolesulfolene **3c** reacted with DMAD at 150 °C to give a complex mixture, which gradually decomposed during attempted purification. Also low solubility of **3c** prevented the reaction at high pressure.

The Diels-Alder reactions of the pyrrolesulfolenes **3** with bis(*tert*-butylsulfonyl)acetylene (BBSA)[18] were next studied (Table 3). The thermal reaction of **3f** (R=Me) with BBSA took place rather easily (100 °C, 2 h) compared with the reaction of **3f** with DMAD (150 °C, 3 h; Entry 5 of Table 2), but [4+2] cycloaddition did not occur. Instead, a Michael type addition at the α-position of the pyrrole ring occurred to give mono-adduct **E** (61% yield) and di-adduct **F** (20% yield). On the other hand, *N*-benzyloxycarbonylpyrrolesulfolene **3b** reacted with BBSA to give an **A** type compound, **G** in 78% yield. It is well known that the use of *N*-electron-withdrawing substituents enhances the reactivity of [4+2] cycloaddition, probably by diminishing the aromatic character of the pyrrole ring.[19] Thus, by using BBSA as a dienophile, the **A** type compound, **G** was obtained selectively. Since **G** (R=CO_2CH_2Ph) could react with a variety of dienophiles, the synthetic potential of **G** appears to be very broad.

These results can be reasonably explained by the mechanism in Scheme 4. The Diels-Alder reaction occurs on the pyrrole moiety to give compounds of type **D'**, which are instantaneously desulfonylated to give compounds **A** (or **G**). Compounds **A** react with another DMAD molecule to give compounds of type **B**. If the substituent on the nitrogen is electron donating , **B** reacts further with another DMAD molecule to give **C** by a double Michael-type reaction or aza-Claisen rearrangement of the ammonium adduct.[20] Under high-pressure

Table 3. Diels-Alder reaction of the pyrrolesulfolene with BBSA

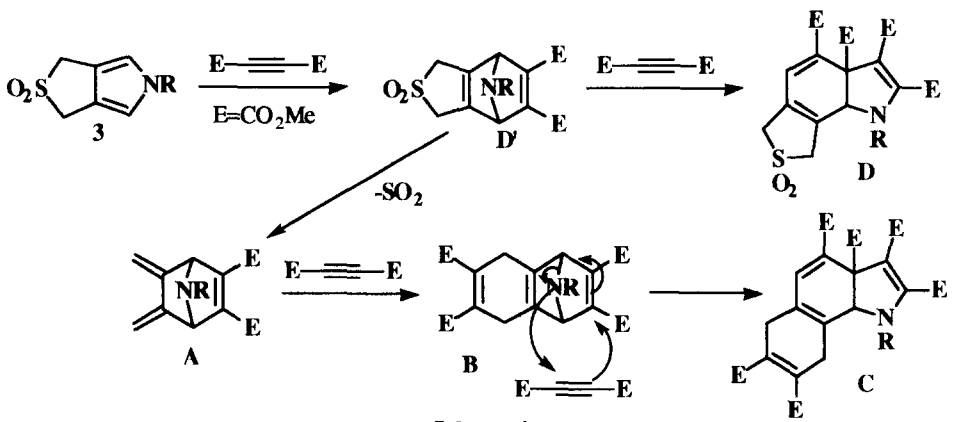


Entry	R		BBSA* (eq)	Solvent	Temp. (°C)	Time (h)	Yield (%) E	F	G	3
1	Me	**3f**	3	toluene	100	2	61	20		
2	CO_2CH_2Ph	**3b**	3	benzene	reflux	2.5			78	5

* BBSA: bis(*tert*-butylsulfonyl)acetylene

condition, compounds **D'** react with another DMAD molecule without desulfonylation to give **D**. The reaction of the isolated **A** (R=CH_2Ph) with DMAD (3 equiv., benzene, 100 °C, 5 h) to give **C** in 91% yield (**A** was recovered in 7% yield) also supports this mechanism.

In conclusion, the pyrrolesulfolenes **3** were prepared by the oxidation of their corresponding pyrroline derivatives **4**. The Diels-Alder reaction of **3** with acetylenic dienophiles provided the new types of compounds **A-G** depending on the reaction conditions and *N*-substituents. These results show that the pyrrolesulfolenes **3** have a wide aplicability to the synthesis of multifunctional multicyclic compounds.



Scheme 4

EXPERIMENTAL SECTION

The melting points (Yamaco Micro Melting Point Apparatus) are uncorrected. The ^1H NMR was recorded in $CDCl_3$ at 400 MHz (JEOL GSX-400) unless otherwise stated, and the chemical shifts are expressed in ppm relative to tetramethylsilane (TMS). Column chromatography was performed on silica gel (Wakogel C-300). Tetrahydrofuran (THF) was distilled from sodium / benzophenone just before use. CH_2Cl_2 was distilled from CaH_2 under argon. All reactions were conducted under an argon atmosphere unless otherwise stated.

5-Benzyl-3,4,5,6-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxide (4a) 3,4-Bis(bromomethyl)-2,5-dihydrothiophene 1,1-dioxide[7] (2.32 g, 7.63 mmol) and benzylamine (2.92 ml, 19.1 mmol) in MeCN (160 ml) were stirred at room temperature for 4 h. After evaporation of the solvent, AcOEt (50 ml) and 1 N NaOH (60 ml) were added to the residue and the aqueous layer was extracted with AcOEt (2 × 50 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was recrystallized from MeOH to give colorless needles (1.14 g, yield 60%). mp 104-105 °C (lit.[11] 100 °C). ^{1}H NMR δ 3.61 (4H, s), 3.78 (4H, t, J=1.5 Hz), 3.88 (2H, s), 7.26-7.34 (5H, m). MS (m/e): 249 ($M^{\oplus}$), 185 ($M^{\oplus}$-SO_2). HRMS calcd for $C_{13}H_{15}NO_2S$: 249.0822, found: 249.0819.

5-Benzyloxycarbonyl-3,4,5,6-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxide (4b) A solution of **4a** (2.00 g, 8.03 mmol) in benzene (15 ml) was treated with benzyl chloroformate (30-35% in toluene) (10.0 ml, ~18 mmol) at room temperature for 3 h. After adding brine-$NaHCO_3$ solution, the resulting mixture was extracted with CH_2Cl_2 (3 × 15 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (hexane:AcOEt=3:1) provided **4b** (1.82 g, yield 77%) as colorless cubes (recrystallized from benzene). mp 136-137 °C (lit.[11] 134 °C). ^{1}H NMR δ 3.82 (2H, s), 3.86 (2H, s), 4.30 (4H, s), 5.18 (2H, s), 7.30-7.38 (5H, m). MS (m/e): 229 ($M^{\oplus}$-SO_2), 138. Anal. calcd for $C_{14}H_{15}NO_4S$: C, 57.32%; H, 5.15%; N, 4.77%. Found: C, 57.49%; H, 5.15%; N, 4.80%.

3,4,5,6-Tetrahydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxide (4c) α-Chloroethyl chloroformate (0.50 ml, 4.7 mmol) was added to a stirred solution of **4a** (936 mg, 3.76 mmol) in dichloroethane (50 ml) at 0 °C. After stirring for 30 min, the mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by adding 1 N NaOH (4 ml) and the aqueous layer was extracted with CH_2Cl_2 (5 × 20 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (hexane :AcOEt=1:1) provided the chloroethyl carbamate (955 mg, yield 96%) as a colorless oil. ^{1}H NMR δ 1.83 (3H, d, J=5.80 Hz), 3.84-3.88 (4H, m), 4.27-4.40 (4H, m), 6.60 (1H, q, J=5.80 Hz). MS (m/e): 265, 267 ($M^{\oplus}$). HRMS calcd for $C_9H_{12}NO_4SCl$: 265.0175, found: 265.0190.

MeOH (15 ml) was added to the above compound (146 mg, 0.55 mmol) and the resulting solution was stirred for 1 h at 50 °C and then evaporated in vacuo. After adding 1 N NaOH (2 ml), the resulting mixture was extracted with CH_2Cl_2 (6 × 12 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give **4c** (62 mg, yield 71%) as colorless needles (recrystallized from CH_2Cl_2:hexane=1:1). mp 115-116 °C (dec.). ^{1}H NMR δ 1.85 (1H, s), 3.82-3.85 (8H, m). ^{13}C NMR δ 53.20 (CH_2), 56.12 (CH_2), 133.51 (C). MS (m/e): 159 ($M^{\oplus}$), 95 ($M^{\oplus}$-SO_2). HRMS calcd for $C_6H_9NO_2S$: 159.0354, found: 159.0361.

3,4,5,6-Tetrahydro-5-(*p*-tolylsulfonyl)-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxide (4d) A solution of **4c** (340 mg, 2.14 mmol) in pyridine (20 ml) was treated with *p*-toluenesulfonyl chloride (489 mg, 2.57 mmol) for 90 min. After addition of 1 N NaOH (6 ml), the mixture was extracted with $CHCl_3$ (6 × 15 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give **4d** (620 mg, yield 93%) as colorless needles (recrystallized from AcOEt). mp 164-165 °C (dec.). ^{1}H NMR δ 2.46 (3H, s), 3.75 (4H, t, J=1.5 Hz), 4.20 (4H, s), 7.36 (2H, dd, J=0.6, 8.6 Hz), 7.73 (2H, m). MS (m/e): 313 ($M^{\oplus}$), 249 ($M^{\oplus}$-SO_2). HRMS calcd for $C_{13}H_{15}NO_2S$ ($M^{\oplus}$-SO_2): 249.0823, found: 249.0830.

5-Benzoyl-3,4,5,6-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxide (4e) Compound **4c** (142 mg, 0.89 mmol), benzoyl chloride (0.125 ml, 1.07 mmol), and 40% K_2CO_3 (1.7 ml) in $CHCl_3$ (14 ml) were stirred for 3 h. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (6 × 14 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give **4e** (233 mg, yield 99%) as colorless needles (recrystallized from benzene). mp 154.5-155.2 °C. ^{1}H NMR δ 3.79 (2H, s), 3.91 (2H, s), 4.31 (2H, s), 4.56 (2H, s), 7.42-7.53 (5H, m). MS (m/e): 263 ($M^{\oplus}$), 199 ($M^{\oplus}$-SO_2). HRMS calcd for

$C_{13}H_{13}NO$ ($M^{\oplus}$-SO_2): 199.0996, found: 199.0984.

5-Benzyl-3,5-dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxide (3a) A solution of **4a** (573 mg, 2.30 mmol) in 1,4-dioxane (30 ml) was treated with DDQ (627 mg, 2.76 mmol) for 3 h. After concentration, brine (50 ml) and CH_2Cl_2 (50 ml) were added to the residue. Aq. $NaHCO_3$ was added to this for neutralization and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (hexane:AcOEt=1:1) provided **3a** (568 mg, yield 100%) as colorless needles (recrystallized from benzene:CCl_4=1:4). mp 136-137 °C. ^{1}H NMR δ 4.15 (4H, s), 5.05 (2H, s), 6.61 (2H, s), 7.13-7.15 (2H, m), 7.31-7.37 (3H, m). ^{13}C NMR δ 53.27 (CH_2), 53.91 (CH_2), 114.12 (C), 116.29 (CH), 127.19 (CH), 128.07 (CH), 128.87 (CH), 137.12 (C). MS (m/e): 247 ($M^{\oplus}$), 183 ($M^{\oplus}$-SO_2). Anal. calcd for $C_{13}H_{13}NO_2S$: C, 63.14%; H, 5.30%; N, 5.69%. Found: C, 63.04%; H, 5.26%; N, 5.41%.

5-Benzyloxycarbonyl-3,5-dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxide (3b) A solution of **4b** (50 mg, 0.17 mmol) in benzene (3 ml) was treated with CMD-U (445 mg) for 4 days. After filtration, the insoluble material was washed with acetone. The combined filtrate was concentrated and the residue was purified by column chromatography (hexane:AcOEt=8:1-2:1) to provid **3b** (29 mg, yield 59%) (86% based on the consumed **4b**) and **4b** (15.5 mg, 31%). **3b** as colorless needles (recrystallized from hexane:AcOEt=5:1). mp 125-126 °C. ^{1}H NMR δ 4.11 (4H, d, J=0.9 Hz), 5.38 (2H, s), 7.25 (2H, t, J=0.9 Hz), 7.38-7.42 (5H, m). ^{13}C NMR δ 52.30 (CH_2), 69.56 (CH_2), 115.44 (CH), 118.23 (C), 128.53 (CH), 128.82 (CH), 129.01 (CH), 134.38 (C), 149.66 (C). MS (m/e): 291 ($M^{\oplus}$), 227 ($M^{\oplus}$-SO_2). Anal. calcd for $C_{14}H_{13}NO_4S$: C, 57.72%; H, 4.50%; N, 4.83%. Found: C, 57.44%; H, 4.52%; N, 4.67%.

3,5-Dihydro-5-(*p*-tolylsulfonyl)-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxide (3d) The same procedure as described for **3b** was used. Column chromatography (CH_2Cl_2:acetone=80:1) provided **3d** (yield 50%) and **4d** (22%). **3d** as colorless needles (recrystallized from hexane:CH_2Cl_2=1:2). mp 208-209 °C. ^{1}H NMR δ 2.43 (3H, s), 4.10 (4H, d, J=0.6 Hz), 7.12 (2H, t, J=0.6 Hz), 7.32-7.34 (2H, m), 7.75-7.78 (2H, m). ^{13}C NMR δ 21.65 (CH_3), 52.26 (CH_2), 115.81 (CH), 119.11 (C), 127.09 (CH), 130.30 (CH), 135.32 (C), 145.85 (C). MS (m/e): 311 ($M^{\oplus}$), 247 ($M^{\oplus}$-SO_2). Anal. calcd for $C_{13}H_{13}NO_4S_2$: C, 50.15%; H, 4.21%; N, 4.52%. Found: C, 50.20%; H, 4.09%; N, 4.38%.

5-Benzoyl-3,5-dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxide (3e) The same procedure as described for **3b** was used. Column chromatography (hexane:AcOEt=5:1-1:1) provided **3e** (yield 54%) and **4e** (41%). **3e** as colorless needles (recrystallized from hexane:$CHCl_3$=4:1). mp 197-198 °C. ^{1}H NMR δ 4.18 (4H, d, J=0.9 Hz), 7.27 (2H, t, J=0.9 Hz), 7.52-7.56 (2H, m), 7.63-7.67 (1H, m), 7.73-7.75 (2H, m). ^{13}C NMR δ 52.35 (CH_2), 116.57 (CH), 118.83 (C), 128.73 (CH), 129.51 (CH), 132.33 (C), 132.86 (CH), 167.21 (C). MS (m/e): 261 ($M^{\oplus}$), 197 ($M^{\oplus}$-SO_2). Anal. calcd for $C_{13}H_{11}NO_3S$: C, 59.76%; H, 4.24%; N, 5.36%. Found: C, 59.59%; H, 4.17%; N, 5.29%.

3,5-Dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxide (3c) A solution of **3b** (412 mg, 1.42 mmol) in THF (40 ml) was treated with 5% Pd/C (50 mg) under hydrogen atmosphere for 24 h. After filtration, the filtrate was concentrated to provide **3c** (222 mg, yield 100%) as colorless rhombuses (recrystallized from MeOH). mp 235-240 °C (dec.). ^{1}H NMR (CD_3OD) δ 4.15 (4H, s), 6.72 (2H, s). ^{13}C NMR (CD_3OD) δ 54.05 (CH_2), 113.93 (CH), 114.22 (C). MS (m/e): 157 ($M^{\oplus}$), 93 ($M^{\oplus}$-SO_2). Anal. calcd for $C_6H_7NO_2S$: C, 45.85%; H, 4.49%; N, 8.95%. Found: C, 46.12%; H, 4.43%; N, 8.71%.

3,5-Dihydro-5-methyl-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxide (3f) To a solution of 3,4-bis(bromomethyl)-2,5-dihydrothiophene 1,1-dioxide (1.82 g, 6.00 mmol) in MeCN (30 ml) was added methylamine (40% MeOH solution) (2.04 ml, 19.5 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 90

min. After evaporation of the solvent, CH_2Cl_2 (30 ml) and 1 N NaOH (15 ml) were added to the residue and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was dissolved in benzene (40 ml) and treated with DDQ (1.86 g, 7.87 mmol) for 2 h. After addition of 1 N NaOH (20 ml), the mixture was extracted with CH_2Cl_2 (5 × 30 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (hexane:AcOEt=2:1) provided **3f** (271 mg, yield 26%) as colorless needles (recrystallized from hexane:AcOEt= 2:1). mp 130-131 °C. ^{1}H NMR δ 3.67 (3H, s), 4.15 (4H, s), 6.53 (2H, s). ^{13}C NMR δ 36.66 (CH_3), 53.27 (CH_2), 113.67 (C), 116.89 (CH). MS (m/e): 171 ($M^{\oplus}$), 107 ($M^{\oplus}$-SO_2). Anal. calcd for $C_7H_9NO_2S$: C, 49.11%; H, 5.30%; N, 8.22%. Found: C, 49.31%; H, 5.21%; N, 7.97%.

Diels-Alder reaction of 3a with DMAD at 100 °C (Entry 1 of Table 2) A solution of **3a** (52 mg, 0.21 mmol) and DMAD (0.076 ml, 0.63 mmol) in benzene (1 ml) was heated at 100 °C for 4 h in a sealed tube. After concentration, the residue was purified by column chromatography (hexane:AcOEt=8:1-2:1) to give **A** (R=CH_2 Ph) (19.2 mg, yield 28%), **C** (R=CH_2Ph) (60 mg, yield 47%), and **3a** (7.7 mg, 15%). **A** (R=CH_2Ph) as a colorless oil. ^{1}H NMR δ 3.47 (2H, s), 3.79 (6H, s), 4.39 (2H, s), 5.29 (2H, s), 5.50 (2H, s), 7.25-7.34 (5H, m). MS (m/e): 325 ($M^{\oplus}$). HRMS calcd for $C_{19}H_{19}NO_4$: 325.1313, found: 325.1309. **C** (R=CH_2Ph) as a yellow oil. ^{1}H NMR δ 2.81-2.93 (1H, m), 3.04-3.20 (3H, m), 3.57 (3H, s), 3.65 (3H, s), 3.74 (3H, s), 3.78 (6H, s), 3.85 (3H, s), 4.21 (1H, d, J=15.9 Hz), 4.35 (1H, d, J=15.9 Hz), 4.66 (1H, s), 6.85 (1H, s), 7.22-7.36 (5H, m). MS (m/e): 609 ($M^{\oplus}$). HRMS calcd for $C_{31}H_{31}NO_{12}$: 609.1847, found: 609.1854.

Diels-Alder reaction of 3a with DMAD at 12 kbar (Entry 4 of Table 2) The Teflon tube containing **3a** (100 mg, 0.40 mmol), DMAD (0.149 ml, 1.20 mmol), and CH_2Cl_2 (1.3 ml) was placed in a high-pressure reactor and pressurized to 12 kbar. After 48 h, the pressure was released and the reaction mixture was concentrated. Column chromatography (hexane:AcOEt=1:2) provided **D** (R=CH_2Ph) (81 mg, yield 38%), and **C** (R=CH_2Ph) (4.9 mg, yield 2%). **D** (R=CH_2Ph) as a colorless powder (recrystallized from hexane:CH_2Cl_2= 2:1). mp 140 °C (dec.). ^{1}H NMR δ 3.60 (3H, s), 3.64 (3H, s), 3.74-3.99 (4H, m), 3.77 (3H, s), 3.90 (3H, s), 4.05 (1H, d, J=15.6 Hz), 4.37 (1H, d, J=15.6 Hz), 4.81 (1H, s), 6.87 (1H, s), 7.21-7.25 (2H, m), 7.33-7.40 (3H, m). MS (m/e): 531 ($M^{\oplus}$), 467 ($M^{\oplus}$-SO_2). HRMS calcd for $C_{25}H_{25}NO_{10}S$: 531.1200, found: 531.1198.

Diels-Alder reaction of 3f with DMAD at 150 °C (Entry 5 of Table 2) A solution of **3f** (40 mg, 0.23 mmol) and DMAD (0.086 ml, 0.69 mmol) in benzene (0.8 ml) was heated at 150 °C for 3 h in a sealed tube. After concentration, the residue was purified by column chromatography (hexane:AcOEt=1:2) to give **C** (R=Me) (89 mg, yield 73%) as a yellow powder (recrystallized from hexane:CH_2Cl_2=2:1). mp 207-209 °C. ^{1}H NMR δ 2.76 (3H, s), 3.09-3.36 (4H, m), 3.67 (3H, s), 3.73 (3H, s), 3.77 (3H, s), 3.80 (3H, s), 3.81 (3H, s), 3.89 (3H, s), 4.40 (1H, s), 6.98 (1H, s). MS (m/e): 533 ($M^{\oplus}$). HRMS calcd for $C_{25}H_{27}NO_{12}$: 533.1496, found: 533.1513.

Diels-Alder reaction of 3b with DMAD at 150 °C (Entry 6 of Table 2) A solution of **3b** (58 mg, 0.20 mmol) and DMAD (0.073 ml, 0.60 mmol) in benzene (1 ml) was heated at 150 °C for 13 h in a sealed tube. After concentration, the residue was purified by column chromatography (hexane:AcOEt=3:1) to give **B** (R=CO_2 CH_2Ph) (87 mg, yield 85%) as a colorless oil. ^{1}H NMR δ 3.07-3.23 (2H, m), 3.29-3.46 (2H, m), 3.76 (6H, s), 3.80 (6H, s), 5.09 (2H, s), 5.38 (2H, s), 7.26-7.36 (5H, m). MS (m/e): 511 ($M^{\oplus}$). HRMS calcd for C_{26} $H_{25}NO_{10}$: 511.1477, found: 511.1469.

Diels-Alder reaction of 3b with DMAD at 12 kbar (Entry 7 of Table 2) The Teflon tube containing **3b** (50 mg, 0.17 mmol), DMAD (0.063 ml, 0.51 mmol), and CH_2Cl_2 (1.6 ml) was placed in a high-pressure reactor and pressurized to 12 kbar. After 48 h, the pressure was released and the reaction mixture was

concentrated. Column chromatography (hexane:AcOEt=4:1-1:1) provided **B** (R=CO_2CH_2Ph) (46 mg, yield 52%), and **3b** (8 mg, 16%).

Diels-Alder reaction of 3d with DMAD at 170 °C (Entry 8 of Table 2) A solution of **3d** (40 mg, 0.13 mmol) and DMAD (0.047 ml, 0.38 mmol) in benzene (0.8 ml) was heated at 170 °C for 14 h in a sealed tube. After concentration, the residue was purified by column chromatography (hexane:AcOEt=4:1) to give **B** (R=Ts) (66 mg, yield 97%) as a colorless oil. ^{1}H NMR δ 2.38 (3H, s), 2.93-3.12 (4H, m), 3.76 (6H, s), 3.78 (6H, s), 5.25 (2H, s), 7.26-7.29 (2H, m), 7.56-7.59 (2H, m). MS (m/e): 531 ($M^{\oplus}$). HRMS calcd for $C_{25}H_{25}NO_{10}S$: 531.1200, found: 531.1201.

Diels-Alder reaction of 3e with DMAD at 170 °C (Entry 9 of Table 2) A solution of **3e** (40 mg, 0.15 mmol) and DMAD (0.057 ml, 0.46 mmol) in benzene (0.8 ml) was heated at 170 °C for 8 h in a sealed tube. After concentration, the residue was purified by column chromatography (hexane:AcOEt=2:1) to give **B** (R=COPh) (73 mg, yield 99%) as a colorless oil. ^{1}H NMR δ 3.06-3.63 (4H, m), 3.77 (3H, s), 3.79 (3H, s), 3.81 (3H, s), 3.87 (3H, s), 5.40 (1H, s), 5.77 (1H, s), 7.41-7.47 (2H, m), 7.49-7.57 (3H, m). MS (m/e): 481 ($M^{\oplus}$). HRMS calcd for $C_{25}H_{23}NO_9$: 481.1373, found: 481.1368.

Diels-Alder reaction of 3f with BBSA at 100 °C (Entry 1 of Table 3) A solution of **3f** (50 mg, 0.29 mmol) and BBSA (233 mg, 0.87 mmol) in toluene (1 ml) was heated at 100 °C for 2 h in a sealed tube. After concentration, the residue was purified by column chromatography (benzene:AcOEt=8:1) to give **F** (R=Me) (41 mg, yield 20%) and **E** (R=Me) (78 mg, yield 61%). **E** (R=Me) as a yellow powder (recrystallized from hexane:CH_2Cl_2=2:1). mp 204-205 °C. ^{1}H NMR δ 1.28 (9H, s), 1.40 (9H, s), 3.72 (3H, s), 4.13-4.23 (3H, m), 4.38 (1H, d, J=15.3 Hz), 6.83 (1H, s), 7.74 (1H, s). MS (m/e): 437 ($M^{\oplus}$). HRMS calcd for $C_{17}H_{27}NO_6S_3$: 437.1000, found: 437.0999. **F** (R=CH_3) as yellow needles (recrystallized from hexane: CH_2Cl_2=2:1). mp 268 °C (dec.). ^{1}H NMR δ 1.34 (18H, s), 1.37 (18H, s), 3.74 (3H, s), 4.10 (2H, d, J=15.6 Hz), 4.53 (2H, d, J=15.6 Hz), 7.83 (2H, s). MS (m/e): 703 ($M^{\oplus}$). HRMS calcd for $C_{27}H_{45}NO_{10}S_5$: 703.1647, found: 703.1633.

Diels-Alder reaction of 3b with BBSA at 80 °C (Entry 2 of Table 3) A solution of **3b** (30 mg, 0.10 mmol) and BBSA (82 mg, 0.31 mmol) in benzene (1 ml) was refluxed for 4 h. After concentration, the residue was purified by column chromatography (hexane:AcOEt=8:1) to give **G** (R=CO_2CH_2Ph) (40 mg, yield 78%) and **3b** (1.5 mg, 5%). **G** (R=CO_2CH_2Ph) as a colorless oil. ^{1}H NMR δ 1.44 (18H, s), 5.13 (2H, s), 5.50 (4H, s), 5.62 (2H, s), 7.32-7.38 (5H, m). MS (m/e): 493 ($M^{\oplus}$). HRMS calcd for $C_{24}H_{31}NO_6S_2$: 493.1593, found: 493.1605.

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