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Diels–Alder reactions of pyridinone *o*-quinodimethanes generated from substituted sulfolene[3,4-*c*]pyridin-4(1*H*)-ones

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Abstract—1-Benzyl-3-(bromomethyl)-2(1*H*)-pyrazinone was converted to [3,4-*c*] sulfolene pyridinone **8a** and further (1- or 3-) substituted derivatives having a dienophilic side chain on the sulfolene ring. Thermolytic extrusion of sulfur dioxide from *o*-QDM precursor **8** led to generation of 3,4-dimethylene-2(1*H*)-pyrazinone **9**, which was reacted in situ with various dienophiles. Thermolysis of the substituted precursors resulted in intramolecular cycloaddition of the corresponding *o*-QDM intermediates

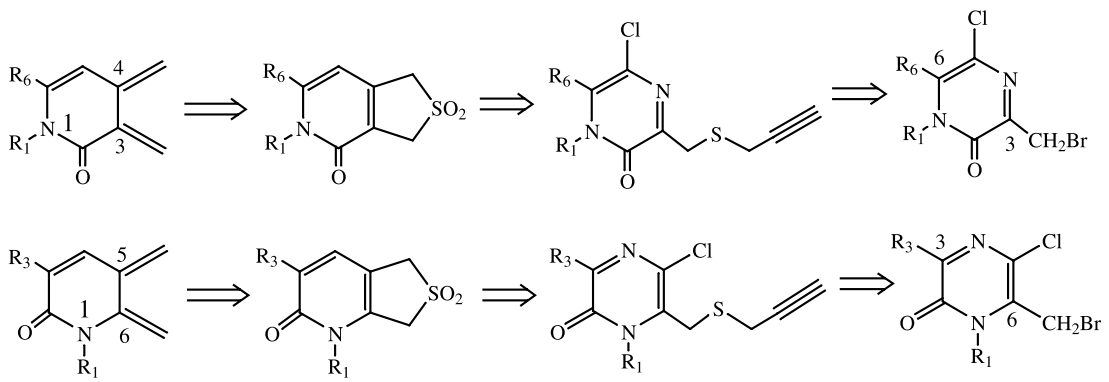
1. Introduction

In the last decade much interest has centred around heteroaromatic *o*-quinodimethanes (*o*-QDM), which are used mostly as diene components in Diels–Alder reactions.[1] These reactive intermediates can be generated in situ by various routes,[2] amongst which thermal extrusion of SO_2 from sulfolene-fused heterocyclic precursors constitutes the most versatile method.[3] As outlined in our previous communication,[4] we used the latter approach to generate both 5,6-dimethylene-5,6-dihydro- and the isomeric 3,4-dimethylene-3,4-dihydro-2(1*H*)-pyridinone *o*-QDM intermediates from, respectively [3,4-*b*]-fused and [3,4-*c*]-fused sulfolene pyridinone precursors. The two precursor types in turn are accessible by intramolecular cycloaddition of either 6-[(2-propynylsulfanyl)methyl] or 3-[(2- propynylsulfanyl)-methyl] substituted pyrazinones (Scheme 1).

Here we give a full account on the synthesis of variously substituted 3,4-dimethylene-3,4-dihydro-2(1*H*)-pyridinone *o*-QDM intermediates and their inter- and intramolecular Diels–Alder reactions, providing access to several unknown ring-fused pyridinones. Although monocyclic pyridinone derivatives are well known for a wide range of biological activities,[5] saturated polycyclic analogues remain largely unexplored.

2. Results and discussion

As indicated in our retrosynthetic analysis (Scheme 1), our sequence starts with the preparation of a [3,4-*c*]-fused sulfolene pyridinone as the *o*-QDM precursor. Subsequent thermolysis affords the corresponding 3,4-dimethylene *o*-QDM intermediate, which is trapped in situ by reaction



Scheme 1. Generation of 5,6- and 3,4-dimethylene dihydro-2(1*H*)-pyridinone *o*-QDM via extrusion of SO_2 from sulfolene pyridinone precursors; these are prepared by cycloaddition of 6- and 3-[(2-propynylsulfanyl)methyl] substituted pyrazinones.

Keywords: *ortho*-quinodimethane; pyridinone; Diels–Alder reaction.

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with various dienophiles. Next we describe regioselective electrophilic substitutions of the precursor at either the more or less acidic α-position of the sulfone group, which allows for attachment of some dienophilic side chains. Finally we examine the scope of the intramolecular Diels–Alder reactions proceeding upon thermolysis of the 1- and 3-substituted precursors.

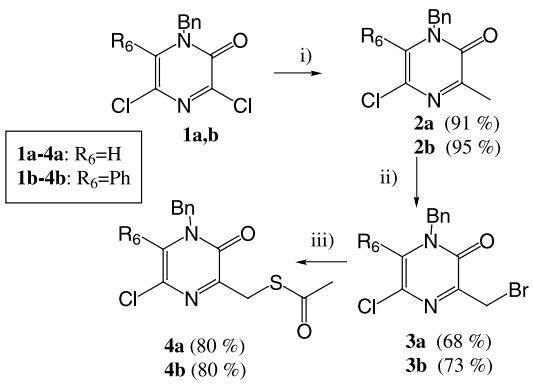
2.1. Synthesis of the pyridinone *ortho*-quinodimethane precursor

According to our synthetic plan, pyrazinones **1a**,**b** were subjected to Stille coupling using $Sn(CH_3)_4$ to introduce a methyl group at the reactive 3-position.[6] Subsequent bromination of the 3-methyl derivatives **2a**,**b** afforded compounds **3a**,**b** along with the dibrominated side product (10%). Final substitution of bromides **3a**,**b** with thiolacetic acid furnished thioesters **4a**,**b** in 80 % yield (Scheme 2).

The thiolate anions generated by treatment of **4a**,**b** with sodium methoxide in methanol were alkylated in situ by adding 3 equiv. of propargyl bromide to produce thioethers **5a**,**b** (Scheme 3). Subsequent intramolecular Diels–Alder reaction was effected by heating **5a**,**b** in dry toluene at reflux temperature. This afforded dihydrothienopyridinone **7a** and the dihydrothienopyridine **7b** as the exclusive products resulting from cycloreversion of the intermediate adducts. The preferential loss of isocyanate instead of cyanogen chloride when R_6=Ph is in agreement with our previous work on *N*-substituted pyrazinones.[6–7] Final oxidation of thienopyridin(on)es **7a**,**b** with *meta*-chloroperoxybenzoic acid (*m*-CPBA) furnished the [3,4-*c*]-fused sulfolene pyridinone **8a** and sulfolene pyridine **8b** in 45% overall yield starting from thioesters **4a**,**b**.

2.2. Generation of pyridinone *ortho*-quinodimethane (*o*-QDM) and application in intermolecular Diels–Alder reactions

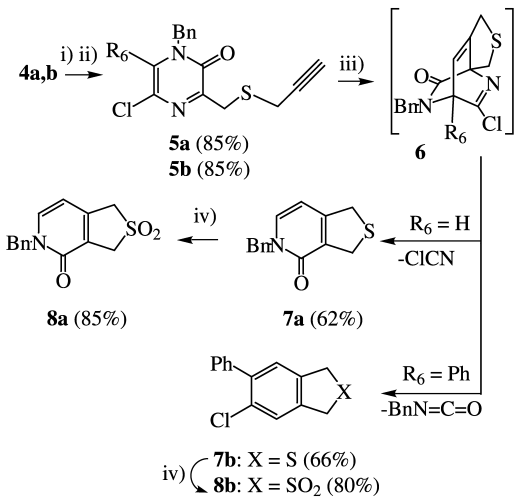
To study the reactivity and regioselectivity of the pyridinone *o*-QDM system in cycloaddition reactions, different types of dienophiles—symmetric and non-symmetric, electron-deficient, neutral and electron-rich -, were applied, i.e. *N*-phenylmaleimide (NPMA), dimethyl maleate, naphthoquinone, dimethyl acetylenedicarboxylate (DMAD), methyl acrylate, nitroethene, dihydrofuran, ethene, and the heterodienophiles *p*-toluenesulfonylcyanide and *N*-(benzylidene)toluenesulfonamide. To this end a solution of precursor **8a** and dienophile (3 equiv.) in *ortho*-dichlorobenzene (*o*-DCB) first was subjected to three freeze-pump-thaw cycles, and then was heated at 150°C in a sealed glass tube to furnish the corresponding adducts **10**-**19** (Scheme 4 and Table 1). The structure and conformational behaviour of the reaction products was determined by ^{1}H NMR analysis.



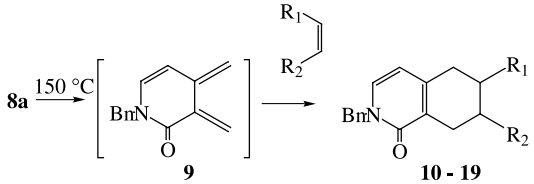
Scheme 2. Synthesis of thioester **4**. *Reagents and conditions*: (i) $SnMe_4$, $Pd(P(Ph)_3)_4$, toluene reflux, 48 h. (ii) 1.2 equiv. NBS, CCl_4, reflux. (iii) 1.2 equiv. $HSCOCH_3$, 3 equiv. NEt_3, THF, rt.

The cycloadduct **10** derived from the reaction with NPMA can exist as two boat conformers **A** and **B** having an axial and equatorial orientation of the maleimide ring (Fig. 1). However, from the ^{1}H NMR spectral data of **10** it appears that conformer **A** is the predominant form. The predominance of either **A** or **B** clearly follows from the differentiation observed between the axial and equatorial protons H-9ax and H-9eq of which the latter was identified by a NOE with H-8. The ^{1}H spectrum further displayed coupling constant values $^3J_{9eq-9a}$=6.4 Hz and $^3J_{9ax-9a}$=3.1 Hz, and also very similar values for the analogous coupling between H-4 and H-3a, i.e. $^3J_{4eq-3a}$=6.8 Hz and $^3J_{4ax-3a}$=2.8 Hz. These small ^3J coupling values preclude a substantial contribution of conformer **B**, in which the axial protons H-4ax and H-9ax exhibit a *trans*-diaxial relationship with the angular protons H-3a and H-9a. Comparable NPMA adducts that were derived from the reaction of pyridine *o*-QDM, also revealed a preferred axial orientation of the maleimide ring.[8]

Reaction of *o*-QDM **9** with dimethyl maleate furnished the expected *cis*-adduct **11** in good yield. By contrast, only the

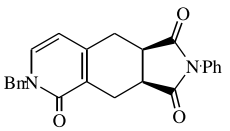
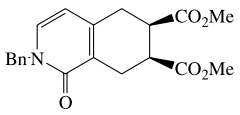
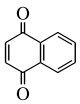
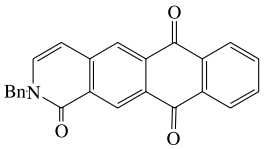
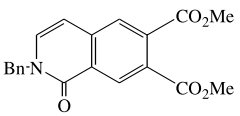
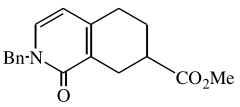
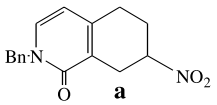
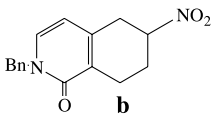
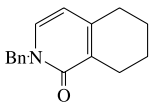
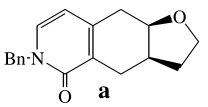
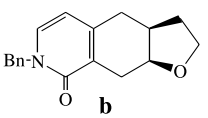
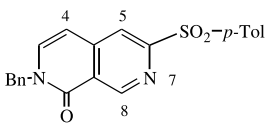
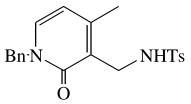


Scheme 3. Synthesis of sulfolene pyridin(on)es. *Reagents and conditions*: (i) 1.3 equiv. NaOMe, MeOH, −20°C. (ii) 3 equiv. propargyl bromide. (iii) Toluene, 110°C, 48 h. (iv) 3 equiv. *m*-CPBA, CH_2Cl_2, rt.



Scheme 4. Generation of pyridinone-*o*-QDM **9** and its cycloaddition with various dienophiles *Reagents and conditions*: see Table 1.

Table 1. Cycloaddition of pyridinone *o*-QDM with various dienophiles

Dienophile	Adduct	Nr (Yield)
NPMA		**10** (65%)
Dimethyl maleate		**11** (70%)
		**12** (65%)
DMAD		**13** (80%)
Methyl acrylate		**14**(80%)
Nitroethene	 **a**  **b**	**15a**,**b** (80%) 4:1
Ethene		**16** (23%)
	 **a**  **b**	**17a**,**b** (ca. 1:1, yield not determined)
TsCN		**18** (69%)
PhCH═NTs		**19**

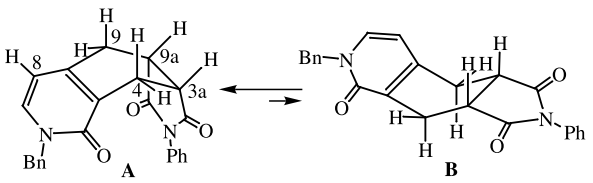


Figure 1. Preferred conformer **A** of adduct **10**.

fully dehydrogenated tetracyclic adduct **12** could be isolated from the reaction with 1,4-naphthoquinone. Addition of DMAD equally afforded the dehydrogenated isoquinolinone derivative **13**, but in this case the initial dihydroisoquinolinone adduct was detected as a transient intermediate by mass spectral analysis of the reaction mixture after reflux under an inert atmosphere.

We next applied the electron-deficient, non-symmetrical dienophiles methyl acrylate and nitroethene. From the reaction with methyl acrylate a single adduct was isolated in good yield. This could be characterised as the 7-regioisomer **14** by ^{1}H NMR analysis using the ASIS technique (aromatic solvent induced shift), i.e. interchanging the solvent from $CDCl_3$ to C_6D_6. In the $CDCl_3$ spectrum, all aliphatic protons were found to absorb in the same region (2–3 ppm), whereas the C_6D_6 spectrum displayed a characteristic downfield shift for the geminal protons H-8 located in *peri*-position of the carbonyl moiety. Unravelling of the coupling patterns corresponding to H-8ax and H-8eq (H-8ax: 3.17 ppm, dd, $^3J_{8ax-7}$=10 Hz, $^2J_{8ax-8eq}$=18 Hz; H-8eq: 2.83 ppm, dd, $^3J_{8eq-7}$=5.5 Hz, $^2J_{8ax-8eq}$=18 Hz) clearly reveals the existence of a single proton H-7 having an axial orientation. Consequently the ester-group is 7-equatorial (Fig. 2).

In opposition to the regioselective cycloaddition of methyl acrylate, a mixture of regioisomers **15a**,**b** (ratio 3:1) was isolated from the thermolysis reaction of precursor **8a** with nitroethene. The isomers could not be separated by column chromatography or HPLC but the structures of the isomeric components again could be assigned on the basis of the downfield signals observed for each of the protons H-8 in the C_6D_6 NMR spectrum of the mixture. Thus, the 7-nitro regiomeric structure **15a** could be attributed to the major component, based on the coupling patterns found for H-8 (δ 3.00, dd, $^3J_{8-7}$=6 Hz, $^2J_{8-8'}$=18.5 Hz) and H-8′ (δ 3.10, dd, $^3J_{8'-7}$=7.5 Hz, $^2J_{8'-8}$=18.5 Hz). For the minor 6-nitro compound **15b** the geminal protons H-8 were detected at 2.28 and 2.73 ppm (dt, $^2J_{8-8}$=19 Hz, $^3J_{8-7}$=5.7 Hz), while the signals for the geminal protons H-5 next to the 6-nitro substituent were found at 2.20 ppm (H-5eq, dd, $^2J_{5ax-5eq}$=16.5 Hz, $^3J_{5-6}$=5.6 Hz) and 2.52 ppm (H-5ax, dd, $^2J_{5ax-5eq}$=16.5 Hz, $^3J_{5-6}$=9.0 Hz).

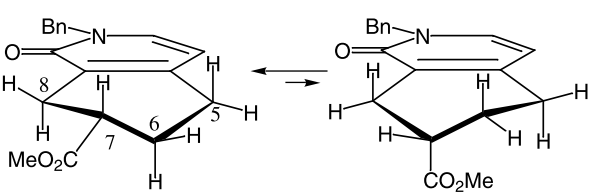


Figure 2. Preferred equatorial orientation of ester group in adduct **14**.

The Diels–Alder reaction of *o*-QDM **9** with ethene was carried out at a gas pressure of 40 atm by heating a solution of precursor **8a** in *o*-dichlorobenzene at 150–160°C for 2 or 3 days. However, the ethene adduct **16** was isolated in only 23% yield and an appreciable amount of the starting sulfolene pyridinone **8a** was recovered. Application of the electron-rich dihydrofuran afforded a complex reaction mixture. Mass spectral and NMR analysis of this mixture indicated the existence of a ca. 1:1 mixture of regiomeric cycloadducts **17**.

In view of the easy reaction and regioselectivity observed with electron-deficient dienophiles, thermolysis of precursor **8a** also was carried out in presence of electron-poor heterodienophiles, i.e. *p*-toluenesulfonylcyanide and *N*-(benzylidene)-*p*-toluenesulfonamide. The former Diels–Alder reaction led to isolation of [2,7]naphthyridinone **18**, and the intermediate non-aromatised adduct could not be detected. The assignment of the naphthyridinone structure was based on ^{1}H and ^{13}C (^{1}H-coupled) NMR analysis and NOE-diff spectra. Proton H-4, which appeared as a doublet at 6.54 ppm, was identified by its NOE-diff interaction with H-5 detected at 7.40 ppm. The ^{13}C–^{1}H-coupled spectrum of **18** further displayed a low $^1J_{C-H}$ value for C-5 ($^1J_{C-H}$=172 Hz) and a high value for C-8 ($^1J_{C-H}$=188 Hz), indicating that the tosylcyanide nitrogen was located in position 7.

The reaction of precursor **8a** with *N*-(benzylidene)-*p*-toluenesulfonamide led to isolation of sulfonamide **19** instead of the expected tetrahydronaphthyridinone. This result might be attributed to traces of water being present in the reaction mixture. Thus, following hydrolytic removal of the *N*-(benzylidene) group, *p*-toluenesulfonamide could add in 1,4-fashion onto the electron-poor methylene group of the pyridinone-*o*-QDM intermediate to yield **19**. However, formation of **19** also might involve alternative cycloaddition of PhCH=NTs onto the α,β-unsaturated carbonyl moiety of *o*-QDM **9** followed by hydrolysis.

As the kinetic outcome of the Diels–Alder reaction can be interpreted successfully by using the frontier molecular orbital (FMO) method, we tried to rationalise the product

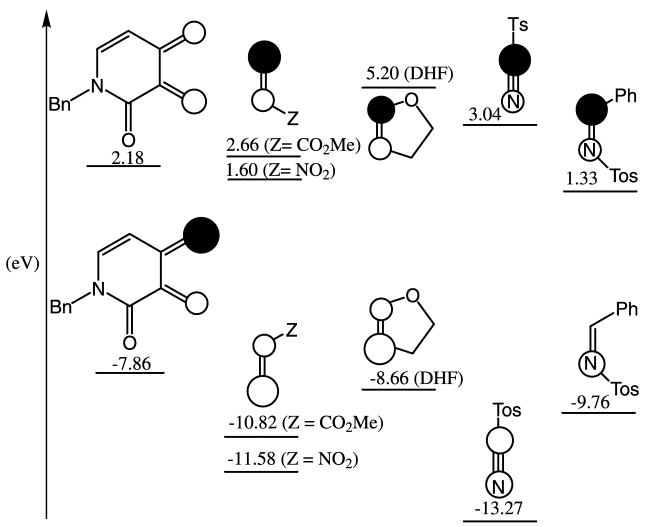


Figure 3. Energy levels calculated for the frontier molecular orbitals.

distribution of cycloadducts formed with non-symmetrical dienophiles. Ab initio calculation of the frontier molecular orbitals was carried out using the Hartree-Fock method with a 3-21G* basis set (Gaussian 98®). From these calculations we derived the energy levels of the HOMO and the LUMO as well as the relative magnitude of the HOMO and LUMO coefficients (Fig. 3).

From the energy diagram it appears that for electron-poor dienophiles the cycloaddition is controlled by the HOMO of the pyridinone *o*-QDM as required for 'normal electron-demand' Diels–Alder reactions. Indeed, the interaction HOMO-*o*-QDM, LUMO-dienophile is largely preferred (3.5 eV for methyl acrylate, 4.3 eV for nitroethene and 4.5 eV for the tosylcyanide). Further inspection of the diagram also reveals that the HOMO-diene coefficient at the 5-methylene position is higher than that for the 6-methylene group. Since the largest coefficient on each addend will become preferentially bonded in the transition state, the experimental outcome of the cycloadditions with methyl acrylate and tosyl cyanide appears to be in line with the calculation. However, it is not clear why a lower regioselectivity is observed for the cycloaddition of nitroethene. For the electron-rich dihydrofuran the 'inverse electron-demand' interaction LUMO-*o*-QDM, HOMO-dienophile is preferred (2.22 eV). Hence, the lack of regioselectivity may be accounted for by the comparable values calculated for the LUMO-diene coefficients on the 5-methylene and 6-methylene ends groups.

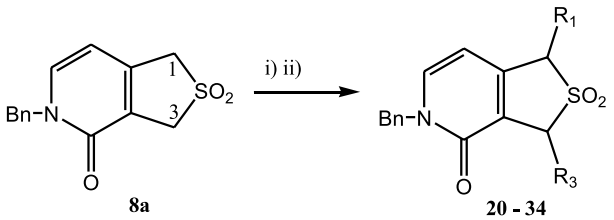
2.3. Substitution of the sulfolene pyridinone precursor

A particular merit of using sulfolene pyridinone precursor **8a** is that it allows for the regioselective introduction of some dienophilic side chains at either the more or less acidic α-position of the sulfone group. When applying 1 equiv. of a strong base or an excess of a weaker base to abstract a proton at the more acidic 1-position, the corresponding monoanion can be generated and functionalised by reaction with a suitable alkylating agent. However, deprotonation at both α-positions can be effected by using 2 equiv. of a stronger base (BuLi), and the resulting 1,3-dianion now can be functionalised at the more reactive 3-position (see scheme heading Table 2).

Substitution at position 1 was accomplished by reaction with tetrabutylammonium fluoride (TBAF) followed by addition of the alkylating reagent. This 1-alkylation was successful with methyl iodide, benzyl bromide, 5-bromo-1-pentene and the α-chloroacetamide $ClCH_2CON(CH_3)CH_2$-$CH{=}CH_2$ but not with the other electrophiles tested. Using other bases and solvents (KH in DMF, BuLi in THF) did not raise the yield significantly.

Substitution at position 3 of the precursor was achieved by using 2.1 equiv. of BuLi, followed by addition of 1 equiv. of the electrophile. This procedure was successful in the reaction with benzyl bromide, 5-bromo-1-pentene, $Br(CH_2)_4CN$, $Br(CH_2)_3CN$, $ClCO_2Me$, and $ClCON(CH_2$-$CH{=}CH_2)_2$ but not with phenyl isocyanate, $Br(CH_2)_2$-$N(Ns)CH_2CH{=}CH_2$, and the Michael acceptors methyl acrylate and acrylonitrile. All attempts to form the dianion with other bases like NaH or KH failed (Table 2). Presumably due to competitive E_2-elimination, rather low yields were obtained for some substitution reactions, e.g. only elimination of HBr was observed upon addition of $Br(CH_2)_2N(Ns)CH_2CH{=}CH_2$ to the dianion generated from precursor **8a**. Ester compound **30** was found to be

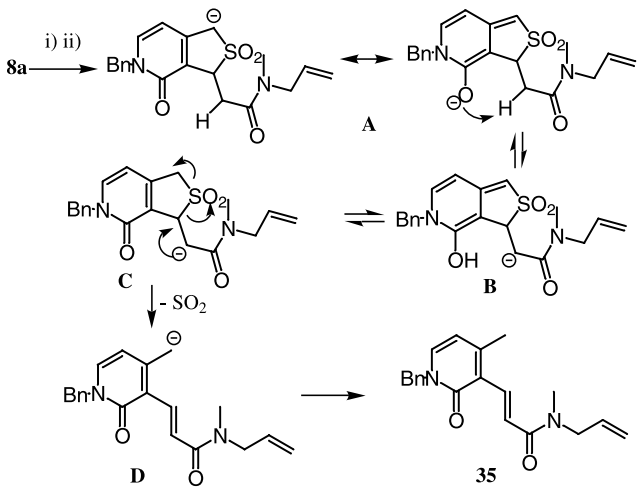
Table 2. Regioselective substitution at the 1- and 3-position of sulfolene pyridinone **8a**



8a **20 - 34**

RX (equiv.)	Product number (condition, yield %)	Substituents
ICH_3 (2)	**20** (A, 70)	R_1=Me, R_3=H
BrBn (2)	**21** (A, 70) (B, 72)	R_1=Bn, R_3=H
$Br(CH_2)_3CH{=}CH_2$ (2)	**22** (A, 56)	R_1=$(CH_2)_3CH{=}CH_2$, R_3=H
$Br(CH_2)_4CN$ (3)	**23** (A, 0) (B, 0) (C, 0)	R_1=$(CH_2)_4CN$, R_3=H
$ClCH_2CON(Me)allyl$ (2)	**24** (A, 63)	R_1=$CH_2CONMeallyl$ R_3=H
$ClCON(allyl)_2$ (2)	**25** (A, 0)	R_1=$CON(allyl)_2$, R_3=H
BrBn (1.1)	**26** (C, 40) (D, 60)	R_1=H, R_3=Bn
$Br(CH_2)_3CH{=}CH_2$ (1.1)	**27** (E, 55)	R_1=H, R_3=$(CH_2)_3CH{=}CH_2$
$Br(CH_2)_4CN$ (1.1)	**28** (E, 58)	R_1=H, R_3=$(CH_2)_4CN$
$Br(CH_2)_3CN$ (1.1)	**29** (E, 44)	R_1=H, R_3=$(CH_2)_3CN$
$ClCO_2Me$ (1.1)	**30** (E, 55)	R_1=H, R_3=CO_2Me
Methyl acrylate (1.1)	**31a** (E, 0) (F, 0)	R_1=H, R_3=$(CH_2)_2$ CO_2Me
Acrylonitril (1.1)	**31b** (E, 0)	R_1=H, R_3=$(CH_2)_2CN$
Phenyl isocyanate	**32** (E, 0)	R_1=H, R_3=CONHPh
$Br(CH_2)_2N(Ns)allyl$ (1.1)	**33** (E, 0) (F, 0)	R_1=H, R_3=$(CH_2)_2N(Ns)allyl$
$ClCON(allyl)_2$ (1.1)	**34** (E, 58)	R_1=H, R_3=$CON(allyl)_2$

(i) THF, Base (ii) RX. *Reagents and conditions*: (A) 1.3 equiv. TBAF, THF, rt. (B) 1.2 equiv. KH, DMF, 0°C. (C) 1.1 equiv. BuLi, THF, −78°C. (D) same as (C)+1 equiv. HMPA. (E) 2.1 equiv. BuLi, THF, −78°C. (F) same as (E)+1 equiv. HMPA.



Scheme 5. Rearrangement occurring upon alkylation of the dianion of **8a** with $ClCH_2CON(CH_3)CH_2CH{=}CH_2$. *Reagents and conditions*: (i) 2.1 equiv. BuLi, THF, −78°C. (ii) 1.1 equiv. *N*-allyl-2-chloro-*N*-methylacetamide.

unstable and easily lost the 3-CO_2Me ester group upon standing for a few days to give back unsubstituted compound.

When applying BuLi (2.1 equiv.) and the α-chloroacetamide $ClCH_2CON(CH_3)CH_2CH{=}CH_2$ to effect substitution at the 3-position of the dianion, rearranged compound **35** was isolated as the only product (Scheme 5). Remarkably, such rearrangement did not occur during conversion of **8a** into the analogous 1-substituted compound **24** (see before).

To explain this result one may invoke a proton transfer that would occur in the initially formed 3-alkylated anion product **A** to give first ion **B** and then the isomeric ion **C**; concomitant expulsion of sulfur dioxide then would provide anion **D** that upon protonation can be converted to the pyridinone product **35**. The rearrangement of **A** may be initiated by the transfer of an acidic hydrogen from the acetamide side chain to the pyridinone carbonyl group, followed by tautomerisation of enol intermediate **B**.

The 1- and 3-substituted compounds were characterised using ^{1}H and ^{13}C NMR spectroscopy. In the NOE-diff-spectra of the 1-benzyl and 1-(4-pentenyl) compounds **21** and **22** strangely a negative NOE-correlation emerged between H-1 and proton H-7 in *peri*-position. We therefore relied on the ^{13}C NMR data to ensure the 1 or 3-position of the substituents. In this respect the δ-values of C-3a and C-7a were of particular interest since a substituent in position 1 was found to induce a large downfield shift for the vicinal carbon C-7a and a smaller upfield shift for C-3a. This tendency is reversed for the 3-substituted sulfone derivatives (Table 3).

Table 3. Selected ^{13}C NMR-data for the 1- and 3-substituted precursors

Compound	δ C-1	δ C-3	δ C-3a	δ C-7a
8	58.4	55.1	122.9	142.6
21	67.9	53.4	121.9	147.0
22	66.9	53.7	121.5	147.2
24	63.5	53.8	121.5	147.3
26	56.1	66.3	126.5	142.6
27	56.8	65.3	127.2	141.7
28	56.6	64.8	126.2	142.1
29	56.8	64.8	126.5	141.9
30	58.3	71.2	121.8	143.1

2.4. The intramolecular Diels–Alder reactions

Having attached a number of dienophilic side chains to either α-position of the sulfone group, we now were able to probe the reactivity of the modified precursors and the corresponding pyridinone *o*-QDM in intramolecular Diels–Alder reactions (IMDA). Our results are discussed with regard to both the synthetic potential of the IMDA approach and the structural properties of the tricyclic pyridinone products.

Thermolysis of the 1-substituted pyridinones **22** and **24** was carried out in *o*-DCB at 150°C. For **22** this reaction furnished a mixture of *cis*-adduct **36** (37%) and *trans*-adduct **37** (30%); as the isomers could not be separated by HPLC the isomeric ratio was determined by ^{1}H NMR analysis. Similarly thermolysis of **24** produced a non-separable mixture of *cis*-lactam **38** (64%) and *trans*-fused product **39** (19%) (Table 4). The assignment of the latter structures was based on the coupling constants found between H-1 and H-4 and the vicinal angular protons. Presumably, expulsion of SO_2 to form the *o*-QDM in each case yields the more stable *E*-isomer due to steric repulsion between the alkylidene and methylene groups in the *Z*-isomer. Consequently, *cis*- and *trans*-adducts must be formed via *endo* and *exo* cycloaddition respectively. Since relatively more *cis*-fused lactam **38** is formed, the *endo* mode of cycloaddition apparently is favoured for the *N*-allylacetamide side chain: this result is in line with previous findings regarding the IMDA of dienophilic side chains having an amide group incorporated into a four atom tether.[9]

Thermolysis of the 3-substituted precursors **27**-**29** and **34** also was done in *o*-DCB at 150°C. (Table 5). The adduct obtained from the 3-(4-pentenyl) derivative **27** displayed a complex ^{1}H NMR spectrum, which according to NOE-diff

Table 4. Thermolysis of 1-substituted precusors

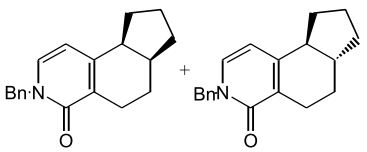
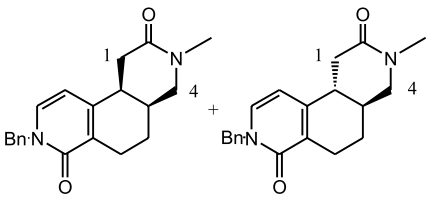
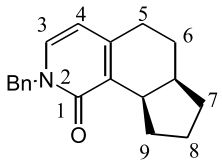
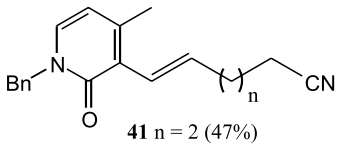
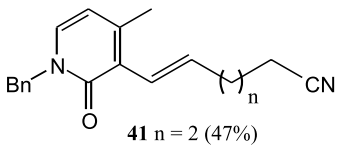
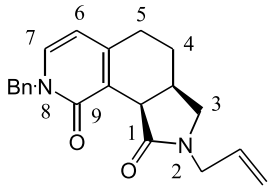
Precursor	Adduct
22	 **36** (37%) **37** (30%)
24	 **38** (64%) **39** (19%)

Table 5. Thermolysis of 3-substituted precursors

Precursor	Adduct
27	 **40** (60%)
28	 **41** n = 2 (47%) **42** n = 1 (42%)
29	 **41** n = 2 (47%) **42** n = 1 (42%)
34	 **43** (65%)

analysis is due to the presence of two slowly interconverting half-chair conformers. This finding is consistent with *cis*-fused structure **40**. Presaturation of H-9a (2.23 ppm) did not result in any observed NOE-effect for adjacent protons; instead a negative signal appeared at 3.04 ppm, which can be ascribed to a saturation transfer of H-9a from one to the other conformer. In agreement with the 3:1 conformational ratio observed, MM+ modeling calculations revealed very similar energies for the two half-chair forms (energy difference lower than 1 kcal/mol).

Apparently, the pyridinone carbonyl function plays an important role in directing the exclusive *endo* mode of cycloaddition. The adduct obtained from the *N*,*N*-diallyl-carboxamide precursor **34** also was characterised as a *cis*-fused tricyclic structure **43** as shown by the doublet absorption of H-9b (δ 4.10, 1H, ^3J=7.3 Hz) and a strong NOE between the angular protons H-9b and H-3a (δ 1.5, 1H, m). However, unlike the carbocyclic analogue **40** *cis*-fused lactam **41** exists as a single half-chair conformer. From MM+ calculations half-chair **A** was shown to be the more stable form as it displays a favourable orthogonal disposition of the pyrazinone carbonyl group and the quasi-axial lactam carbonyl group (Fig. 4). The existence of form **A** and not the opposite half-chair form **B** with parallel carbonyl groups was confirmed by a strong NOE between H-3′ and H-9b and by a ^3J value $\cong$ 0 for protons H-3a and H-3; the latter value reflects a dihedral angle of ca. 90° calculated by MM+.

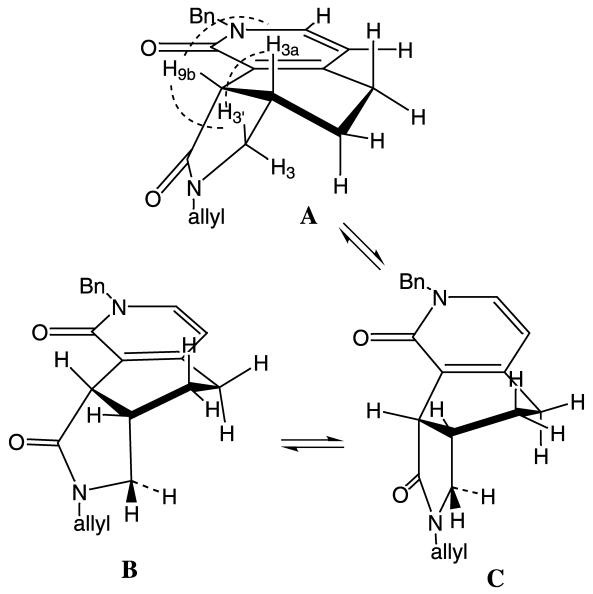
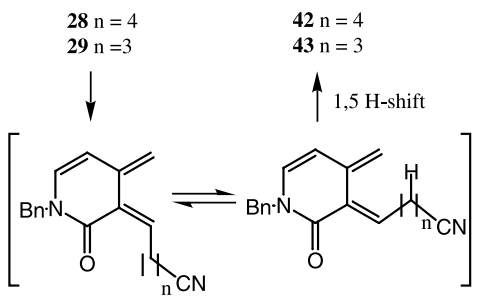


Figure 4. NOE's indicating the presence of the more stable half-chair form **A** and MD simulation of the conversion of half-chair **B** into **A** via twist-boat **C**.

Starting from the highly energetic form **B**, a molecular dynamics (MD) simulation was carried out which revealed the easy conversion of **B** into the other half-chair **A**. This conversion was found to proceed via twist-boat **C** having an energy intermediate between that of **A** and **B**, due to the orthogonal orientation of carbonyl groups already present (Fig. 4).

Although some Diels–Alder reactions involving nitrile dienophiles have been reported,[10] no adduct formation was observed upon thermolysis of the 3-(4-cyanobutyl) and the 3-(4-cyanopropyl) substituted precursors **28** and **29**; instead the pyridinone *o*-QDM intermediates were transformed into the corresponding rearranged products **42** and **43**. Although the *E*-isomer probably is the initial species formed, this can be transformed into the *Z*-isomer, presumably via a pyridinone cyclobutene intermediate; the *Z*-isomer finally undergoes a 1,5-H-shift (Scheme 6).[11] When compared to *p*-toluenesulfonyl cyanide that is subject to intermolecular cycloadition, nitriles **28** and **29** are less electron-deficient; moreover IMDA of these nitriles would require the opposite regiochemistry.



Scheme 6. 1,5-H-shift.

3. Conclusion

From the results presented it follows that [3,4-*c*]sulfolene pyridinones are valuable precursors for the generation of the

corresponding pyridinone *o*-QDM. These *o*-QDM systems can be applied in various inter- and intramolecular Diels–Alder reactions to produce polycyclic pyridinones.

Starting from 2(1*H*)-pyrazinones we developed a synthetic route to [3,4-*c*]sulfolene pyridinone **8a**, which served as a precursor of *o*-QDM **9**. This was generated by heating the precursor at 150°C, and trapped in situ by intermolecular Diels–Alder reactions. Reaction with symmetric, electron-poor dienophiles afforded the corresponding adducts in good yields. Application of non-symmetrical, electron-poor dienophiles led to regioselective addition with methyl acrylate and *p*-toluenesulfonylcyanide, but to a lesser extent with nitroethene. By contrast, cycloaddition of the electron-rich dihydrofuran was not regioselective.

A particular advantage of sulfolene pyridinone precursor **8a** is that it allows for substitution at either the more or less acidic α-position of the sulfone group. Thus, electrophilic attack on the 1-mono- or 1,3-dianion permits regioselective attachment of some dienophilic side chains. Thermolysis of the 1-substituted precursors led to isolation of a mixture of *cis*- and *trans*-fused pyridinone adducts whereas reaction of the 3-substituted precursors exclusively furnished *cis*-fused pyridinone adducts corresponding to *endo* addition of the *E*-*o*-QDM intermediates. Apparently, the nearby pyridinone carbonyl function plays an important role in directing the *endo* addition of 3-substituted precursors.

4. Experimental

Melting points were determined using a Reichert–Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 297 grating IR spectrophotometer and a Perkin–Elmer 1720 Fourier transform spectrometer. Mass spectra were run using a Hewlett–Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10000. For the NMR spectra (δ, ppm) a Bruker Avance 300 and a Bruker AMX 400 spectrometer were used. All NMR spectra were taken up in $CDCl_3$ with TMS as an internal standard unless otherwise stated. Analytical and preparative thin layer chromatography was carried out using Merck silica gel 60 PF-224, for column chromatography 70–230 mesh silica gel 60 (E.M. Merck) was used as the stationary phase. Compounds **1**-**3a**,**b** were synthesized as described in a previous publication.[6]

4.1. General procedure for the synthesis of thioesters 4

To a stirred solution of bromide **3** (0.1 mol) and thiolacetic acid (0.12 mol) in dry THF (500 mL) was added dropwise NEt_3 (0.3 mol) under an inert atmosphere. After completion of the reaction, water (500 mL) was added and the mixture was extracted with CH_2Cl_2 (3×200 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography (Silica gel 5 EtOAc/95 CH_2Cl_2) to afford compounds **4**.

4.1.1. S^1-[(4-Benzyl-6-chloro-3,4-dihydro-3-oxo-2-pyrazinyl)methyl]ethanethioate 4a. Yield: 80%; pale white powder, mp: 83–83.5°C (ethanol); IR (KBr/cm^{-1}): 3063, 1730, 1650; ^{1}H NMR: δ 2.37 (s, 3H, CH_3), 4.27 (s, 2H, CH_2S), 5.05 (s, 2H, CH_2–N), 7.14 (s, 1H, H-6), 7.32–7.38 (m, 5H, H–Ph); ^{13}C NMR: δ 30.1 (CH_3), 31.3 (CH_2S), 52.4 (CH_2–N), 125.6 (C-6), 125.8 (C-5), 128.7 (C–Ph *ortho*), 128.9 (C–Ph *meta*), 129.2 (C–Ph *para*), 133.9 (C–Ph *ipso*), 154.1 (C-3), 155.1 (C-2), 193.8; MS [*m*/*z* (%)]: EI: 308 (20, $M^{+\cdot}$), 266 (81, $M^{+\cdot}-CH_3CO$), 233 (7, $M^{+\cdot}-CH_3COSH$), 175 ($M^{+\cdot}-CH_3CO-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{14}H_{13}ClN_2O_2S$: 308.0386, found: 308.0383; CHN analysis: calcd for $C_{14}H_{13}ClN_2O_2S$: C 54.46, H 4.24, N 9.07; found: C 54.18, H 4.00, N 8.88.

4.1.2. S^1-[(4-Benzyl-6-chloro-5-phenyl-3,4-dihydro-3-oxo-2-pyrazinyl)methyl]-ethanethioate 4b. Compound **4b** was prepared from bromide **3b** in the same way as described for the conversion of **3a** to **4a**. Yield: 80%; white powder; mp: 90.5–91°C (Ethanol); IR (KBr/cm^{-1}): 3051, 1745, 1680; ^{1}H NMR: δ 2.40 (s, 3H, CH_3), 4.38 (s, 2H, CH_2S), 5.50 (s, 2H, CH_2–N), 6.78 (d, 2H, J_o=8 Hz, H–Ph) 7.05 (d, 2H, J_0=8 Hz, H–Ph), 7.20 (m, 3H, H–Ph), 7.37–7.47 (m, 3H, H–Ph); ^{13}C NMR: δ 30. (CH_3), 31.5 (CH_2S), 49.4 (CH_2–N), 137.8 (C-6), 126.1 (C-5), 153.6 (C-3), 154.9 (C-2), 194.0, 135.2 (C-*ipso*), 130.6 (C-*ipso*), 127.3 (C-arom), 127.8 (C-arom), 128.5 (C-arom), 128.8 (C-arom), 129.3 (C-arom), 130.1 (C-arom); MS [*m*/*z* (%)]: CI: 385 (100, MH^+), 343 (25, MH^+-CH_3CO), 309 (18, MH^+-CH_3COSH 91 (5, $C_7H_7^+$); HRMS: calcd for $C_{20}H_{17}ClN_2O_2S$: 384.0699; found: 384.0705.

4.2. General procedure for synthesis of thioethers 5

To a cooled (−20°C) solution of thioester (0.05 mol) in methanol (250 mL) was added under an inert atmosphere 1.3 equiv. of sodium methoxide. After reaction at −20°C for 1 hour 3 equiv. of propargylic bromide were added. The reaction mixture was stirred at rt for 2.5 h and neutralised with a dilute solution of HCl in MeOH. The solution was concentrated, the residue redissolved in CH_2Cl_2 (150 mL), and the CH_2Cl_2 solution washed with water (2×150 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography (silica gel 70% hexane/30% EtOAc) to afford thioether compounds **5**.

4.2.1. 1-Benzyl-5-chloro-3-[(2-propynylsulfanyl)-methyl]-2(1*H*)-pyrazinone 5a. Yield: 85%; yellow oil; IR (NaCl/cm^{-1}): 3301, 2117, 3067, 1587; ^{1}H NMR: δ 2.22 (t, 1H, ^4J=2.5 Hz, ≡CH), 3.35 (d, 2H, ^4J=2.5 Hz, CH_2), 3.92 (s, 2H, 3-CH_2), 5.04 (s, 2H, CH_2–N), 7.25 (s, 1H, H-6), 7.50–7.26 (m, 5H, H–Ph); ^{13}C NMR: δ 18.8, 32.8, 52.4 (CH_2–N), 60.1, 71.2, 80.1, 125.3, 125.8, 128.4, 128.6, 128.9, 134.1, 153.9, 156.0; MS [*m*/*z* (%)]: EI: 304 (1, $M^{+\cdot}$), 269 (42, $M^{+\cdot}-Cl$), 243 (32, $M^{+\cdot}-ClCN$), 234 (21, $M^{+\cdot}-C_3H_2S$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{15}H_{13}ClN_2OS$: 304.0437; found: 304.0429.

4.2.2. 1-Benzyl-5-chloro-6-phenyl-3-[(2-propynylsulfanyl)methyl]-2(1*H*)-pyrazinone 5b. Yield: 85%; yellow oil; IR (NaCl/cm^{-1}): 3057, 2100, 1592; ^{1}H NMR: δ 2.2 (t, 1H, ^4J=2.5 Hz, ≡CH), 3.45 (d, 2H, ^4J=2.5 Hz, CH_2), 4.01

(s, 2H, 3-CH_2), 5.06 (s, 2H, CH_2–N), 6.25 (d, 2H, J_o=8 Hz, H–Ph), 7.01–7.26 (m, 8H, H–Ph); ^{13}C NMR: δ 20.2 (CH_2), 33.1 (CH_2), 48.9 (CH_2–N), 71.1 (CH), 80.1 (C), 118.3, 120.5, 125.8, 127.3, 127.7, 128.4, 128.7, 129.3, 130.0, 130.6, 135.1 (C-*ipso*), 137.5, 154.9, 171.1 (C-2); MS [*m/z* (%)]: CI: 381 (91, MH^+), 309 (100, $MH^+-C_3H_2S$, –H), 248 (16, MH^+–BnNCO), 91 (28, $C_7H_7^+$); HRMS: calcd for $C_{21}H_{17}ClN_2OS$: 380.0750; found: 380.0758.

4.3. General procedure for the thermolysis of thioethers

A solution of thioether (0.04 mol) in dried toluene (300 mL) was refluxed under an inert atmosphere (6–48 h depending on the thioether). The solvent was evaporated and the residue was purified by column chromatography (silica gel, 15% EtOAc/85% CH_2Cl_2) to give cyclic sulfides **7**.

4.3.1. 5-Benzyl-1,3-dihydrothieno[3,4-*c*]pyridin-4(5*H*)-one 7a. Yield: 67%; white crystals, mp: 131.8–132.6°C (CH_2Cl_2/hexane); IR (KBr/cm^{-1}): 3051, 2964, 1651; ^{1}H NMR: δ 4.18 (s, 2H, CH_2), 4.19 (s, 2H, CH_2), 5.12 (s, 2H, CH_2–N), 6.10 (d, 1H, *J*=7 Hz, H-7), 7.19 (d, 1H, *J*=7 Hz, H-6), 7.27–7.30 (m, 5H, H–Ph); ^{13}C NMR: δ 36.8 (C-3), 39.7 (C-1), 52.1 (CH_2–N), 102.0 (C-7), 117.4 (C-3a), 128.0 (C–Ph *para*), 128.3 (C–Ph *ortho*), 128.9 (C–Ph *meta*), 136.1 (C-6), 136.3 (C–Ph *ipso*), 137.9 (C-7a), 160.1; MS [*m/z* (%)]: EI: 243 (70, $M^{+\cdot}$), 152 (60, $M^{+\cdot}-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{14}H_{13}NOS$: 243.0718; found: 243.0715.

4.3.2. 2-Chloro-3-phenyl-5,7-dihydrothieno[3,4-*b*]pyridine 7b. Yield: 66%; unstable yellow oil; IR (NaCl/cm^{-1}): 3051, 2964; ^{1}H NMR: δ 4.10 (s, 2H, CH_2), 4.25 (s, 2H, CH_2), 7.20–7.35 (m, 6H, H-4+H–Ph); MS [*m/z* (%)]: EI: 247 (100, $M^{+\cdot}$), 211 (60, $M^{+\cdot}$–HCl).

4.4. General procedure for the oxidation of cyclic sulfides 7 to form sulfones 8

To a solution of thienopyridinone **7** (0.02 mol) in dry CH_2Cl_2 (150 mL) was added *meta*-chloroperoxybenzoic acid (0.06 mol). The mixture was stirred for 18 h at rt. Then a saturated solution of $NaHCO_3$ (50 mL) was added, and stirring was continued for 4 h. The organic phase was separated and the aqueous phase further extracted with CH_2Cl_2. The combined organic layers were washed with water and dried over $MgSO_4$ and the solvent evaporated. The residue was purified by column chromatography (silica 15% EtOAc/CH_2Cl_2) to afford sulfones **8**.

4.4.1. 5-Benzyl-1,3-dihydro-2,2-dioxothieno[3,4-*c*]pyridin-4(5*H*)-one 8a. Yield: 85%; white crystals, mp 144°C (decomposition); IR (KBr/cm^{-1}): 2968, 1652, 1589, 1316, 1123; ^{1}H NMR: δ 4.26 (s, 2H, CH_2), 4.28 (s, 2H, CH_2), 5.14 (s, 2H, CH_2–N), 6.13 (d, 1H, *J*=7 Hz, H-7), 7.26–7.36 (m, 5H, H-6+H–Ph); ^{13}C NMR: δ 52.3 (CH_2–N), 55.1 (C-3), 58.4 (C-1), 103.3 (C-7), 122.9 (C-3a), 135.5 (C-Ph *ipso*),128.1, 128.3, 128.4, 137.9, 142.6, 158.6; MS [*m/z* (%)]: EI: 275 (9, $M^{+\cdot}$), 211 (40, $M^{+\cdot}-SO_2$), 91 (Bn^+); HRMS: calcd for $C_{14}H_{13}NO_3S$: 275.0616; found: 275.0613; CHN analysis: calcd for $C_{14}H_{13}NO_3S$: C 61.07, H 4.76, N 5.09; found: C 60.90, H 4.55, N 4.95.

4.4.2. 2-Chloro-3-phenyl-5,7-dihydro-6,6-dioxothieno[3,4-*b*]pyridine 8b. Yield: 80%; white powder, mp 208°C (decomposition); IR (KBr/cm^{-1}): 2987, 1545; ^{1}H NMR (DMSO/TMS): δ 4.65 (s, 2H, H-1), 4.69 (s, 2H, H-3), 7.49 (m, 5H, H–Ph), 7.91 (s, 1H, H-7); ^{13}C NMR: δ 55.6 (CH_2), 56.5 (CH_2), 127.9 (C-6), 128.5 (C-arom), 128.6 (C-arom), 129.1 (C-arom), 135.9 (C-7a), 136.4 (C-*ipso*), 137.9 (C-7), 147.9 (C-5), 151.8 (C-3a); MS [*m/z* (%)]: CI: 280 (100, MH^+), 216 (16, MH^+-SO_2), 180 (5, MH^+-SO_2, –HCl); HRMS: calcd for $C_{13}H_{10}ClNO_2S$: 279.7427; found: 279.7421.

4.5. General procedure for intermolecular Diels–Alder reactions

A solution of sulfolene pyridinone (0.2 g, 0.7 mmol) and 5 equiv. of dienophile in *o*-dichlorobenzene (10 mL), contained in a glass tube, was subjected to three freeze-pump-thaw cycle. The glass tube was sealed under vacuum and heated for 12 h at 160°C. After cooling and opening the tube the solvent was removed by Kugelrohr distillation. The adducts were purified by column chromatography.

4.5.1. (3a*R,9a*S**)-6-Benzyl-2-phenyl-3a,4,9,9a-tetrahydro-1*H*-pyrrolo[3,4-*g*]isoquinoline-1,3,5(2*H*,6*H*)-trione 10.** Dienophile: 5 equiv. of *N*-phenylmaleimide. Yield: 65%; yellow crystals, mp: 194–194.8°C (ethanol); IR (KBr/cm^{-1}): 3055, 2983, 1713, 1650; ^{1}H NMR: δ 2.76 (dd, 1H, *J*=6.8, 15.6 Hz, H-4), 2.82 (dd, 1H, *J*=6.4, 14.9 Hz, H-9), 2.99 (dd, 1H, *J*=3.2, 14.9 Hz, H-9), 3.33–3.42 (m, 2H, H-9a+H-3a), 3.49 (dd, 1H, *J*=2.8, 15.6 Hz, H-4), 5.08 (d, 1H, *J*=14.5 Hz, CH_2–N), 5.14 (d, 1H, *J*=14.5 Hz, CH_2–N), 6.05 (d, 1H, *J*=6.8 Hz, H-8), 7.06–7.08 (m, 2H, H–Ph), 7.16 (d, 1H, *J*=6.8 Hz, H-7), 7.23–7.38 (m, 8H, H–Ph); ^{13}C NMR: 22.3 (C-4), 29.2 (C-9), 39.2, 39.3, 52.2 (CH_2), 107.0 (C-8), 125.1 (C-4a), 126.1, 127.8, 127.9, 128.4, 128.8, 128.9, 131.6 (C-*ipso*), 135.3 (C-7), 136.4 (C-*ipso*), 146.4 (C-8a), 160.7 (C-5), 177.7, 177.9; MS [*m/z* (%)]: EI: 384 (100, $M^{+\cdot}$), 293 (2, $M^+-C_7H_7^+$), 237 (5, $M^+-C_6H_5N(CO)_2$), 146 (67, $C_6H_5N(CO)_2$), 91 (69, $C_7H_7^+$); HRMS: calcd for $C_{24}H_{20}N_2O_3$: 384.1474; found: 384.1471.

4.5.2. Dimethyl (6*R,7*R**)2-benzyl-5,6,7,8-tetrahydro-1-oxo-2*H*-isoquinoline-6,7-dicarboxylate 11.** Dienophile: 10 equiv. of methyl acrylate. Yield: 70%; yellow crystals, mp: 115–117°C (CH_2Cl_2/hexane); ^{1}H NMR: δ 2.10–2.33 (m, 1H), 2.50–2.95 (m, 4H), 3.30 (m, 1H), 3.56 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 5.10 (d, 1H, CH_2–N), 5.12 (d, 1H, CH_2–N), 6.10 (d, 1H, *J*=7 Hz, H-4), 7.10 (d, 1H, *J*=7 Hz, H-3), 7.00–7.32 (m, 5H, H–Ph); ^{13}C NMR: 26.1 (CH_2), 28.1 (CH_2), 38.9 (CH), 39.3 (CH) 51.2 (CH_3), 52.0 (CH_2-benzyl), 52.5 (CH_3), 109.0 (C-4), 126.0 (C-8a), 127.6, 128.2, 129.0, 133.0, 136.6 (C-*ipso*), 162.4 (C-1), 174.0, 175.5; MS [*m/z* (%)]: EI: 355 (20, $M^{+\cdot}$), 296 (69, $M^{+\cdot}-C_2H_3O_2$), 264 (15, $M^{+\cdot}-C_7H_7$), 237 (8, $M^{+\cdot}-2\times C_2H_3O_2$), 205 (57, $M^{+\cdot}-C_2H_3O_2$, $-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{20}H_{21}NO_5$: 355.1420; found: 355.1428.

4.5.3. 2-Benzylnaphtho[2,3-*g*]isoquinoline-1,6,11(2*H*)-trione 12. Dienophile: 5 equiv. of 1,4-naphthoquinone. Yield: 65%; yellow crystals, mp: 190–190.5°C (ethanol);

IR (KBr/cm^{-1}): 3067, 1671, 1617; ^{1}H NMR: δ 5.26 (s, 2H, CH_2–N), 6.67 (d, 1H, ^3J=7.2 Hz, H-4), 7.28 (d, 1H, ^3J=7.2 Hz, H-3), 7.30–7.37 (m, 5H, H-arom), 7.83 (dd, 2H, J_o=7 Hz, J_m=2.5 Hz, H-7+H-10), 8.33–8.40 (m, 2H, H-8+H-9), 8.43 (s, 1H, H-12), 9.41 (s, 1H, H-5); ^{13}C NMR: 52.4 (CH_2–N), 106.3 (CH), 126.3 (CH), 127.8 (CH), 128.1 (CH) 128.2 (CH), 128.3 (CH), 128.9 (CH), 129.0 (CH), 129.4 (CH), 129.8 (CH), 134.5 (CH), 135.0 (CH), 135.2 (C), 131.3 (C), 134.1 (C), 135.5 (C), 136.5 (C), 141.2 (C), 162.0 (C-1), 182.1 (CO), 183.3 (CO)); MS [*m*/*z* (%)]: EI: 365 (35, $M^{+\cdot}$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{24}H_{15}NO_3$: 365.1052; found: 365.1049.

4.5.4. Dimethyl 2-benzyl-1-oxo-2*H*-isoquinoline-6,7-dicarboxylate 13. Dienophile: 5 equiv. dimethyl acetylenedicarboxylate. Yield: 80%; colourless oil; IR (NaCl/cm^{-1}): 3011, 2983, 1713, 1650, 1595; ^{1}H NMR: δ 3.93 (s, 3H, CH_3), 3.95 (s, 3H, CH_3), 5.22 (s, 2H, CH_2–N), 6.49 (d, 1H, *J*=7.5 Hz, H-4), 7.22 (d, 2H, *J*=7.5 Hz, H-3), 7.26–7.33 (m, 5H, H–Ph), 7.73 (s, 1H, H-5), 8.91 (s, 1H, H-8); ^{13}C NMR: δ 51.9 (CH_2–N), 52.6 (CH_3), 52.9 (CH_3), 105.5 (C-4), 126.5, 126.8, 127.9, 128.0, 128.9, 130.4, 134.3, 136.1, 139.0, 161.2 (C-1), 166.5, 168.1; MS [*m*/*z* (%)]: EI: 351 (54, $M^{+\cdot}$), 320 (13, $M^{+\cdot}-OCH_3$), 292 (5, $M^{+\cdot}-C_2H_3O_2$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{20}H_{17}NO_5$: 351.1107, Found: 351.1103.

4.5.5. Methyl 2-benzyl-5,6,7,8-tetrahydro-1-oxo-2*H*-isoquinoline-7-carboxylate 14. Dienophile: 10 equiv. of methyl acrylate. Yield: 85%; white crystals, mp: 146–147°C (CH_2Cl_2/hexane); ^{1}H NMR: δ 1.79–1.83 (m, 1H), 2.01–2.12 (m, 1H), 2.58–2.69 (m, 4H), 3.00 (dd, 1H, *J*=10.0, 18.0 Hz, H-8), 3.70 (s, 3H, CH_3), 5.09 (d, 1H, CH_2–N), 5.11 (d, 1H, CH_2–N), 5.91 (d, 1H, *J*=7 Hz, H-4), 7.06 (d, 1H, *J*=7 Hz, H-3), 7.05–7.32 (m, 5H, H–Ph); (C_6D_6) δ 1.51–1.61 (m, 1H, H-6), 1.75–1.79 (m, 1H, H-6), 2.00–2.07 (m, 1H, H-5$_{ax}$), 2.17 (dt, 1H, *J*=18, 5 Hz, H-5$_{eq}$), 2.31–2.35 (m, 1H, H-7), 2.85 (dd, 1H, *J*=5.5, 18.0 Hz, H-8$_{eq}$), 3.17 (dd, 1H, *J*=10.0, 18.0 Hz, H-8$_{ax}$), 3.32 (s, 3H, CH_3), 4.77 (d, 1H, *J*=14.2 Hz, CH_2–N), 4.87 (d, 1H, *J*=14.2 Hz, CH_2–N), 5.37 (d, 1H, *J*=7.0 Hz, H-4), 6.51 (d, 1H, *J*=7.0 Hz, H-3), 7.00–7.15 (m, 3H, H–Ph), 7.17–7.19 (m, 2H, H–Ph); ^{13}C NMR: 24.2, 26.2, 28.1, 38.9 (C-7), 51.6 (CH_3), 51.7 (CH_2-benzyl), 107.6 (C-4), 125.5 (C-8a), 127.7, 128.1, 128.7, 133.0 (C-3), 136.6 (C-*ipso*), 161.9 (C-1), 175.3; MS [*m*/*z* (%)]: EI: 297 (79, $M^{+\cdot}$), 238 (78, $M^{+\cdot}-C_2H_3O_2$), 206 (6, $M^{+\cdot}-C_7H_7$), 146 (31, $M^{+\cdot}-C_2H_3O_2$, $-C_7H_7$, $-H$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{18}H_{14}NO_3$: 297.1365; found: 297.1360.

4.5.6. 2-Benzyl-7-nitro-5,6,7,8-tetrahydro-1(2*H*)-isoquinolinone 15a and 2-benzyl-6-nitro-5,6,7,8-tetrahydro-1(2*H*)-isoquinolinone 15b. Dienophile: 5 equiv. of nitroethene. Yield: 80%; yellow oil; IR (KBr/cm^{-1}): 3071, 2940, 1647, 1589, 1543, 1381; ^{1}H NMR: δ 2.27 (m, 2H, CH_2 **a**+**b**), 2.66 (m, 2H, CH_2 **a**+**b**), 3.14 (m, 2H, CH_2 **a**+**b**), 4.75 (m, 1H, CH **a**+**b**), 5.05 (d, 0.75H, *J*=14.3 Hz, CH_2–N **a**), 5.08 (s, 0.5H, CH_2–N**b**), 5.10 (d, 0.75H, *J*=14.3 Hz, CH_2–N**a**), 5.91 (d, 0.75H, *J*=7.0 Hz, H-4 **a**), 5.93 (d, 0.25H, ^2J=7.0 Hz, H-4 **b**), 7.09 (d, 1H, ^2J=7.0 Hz, H-3 **a**+**b**), 7.22–7.28 (m, 5H, H–Ph **a**+**b**); (C_6D_6/TMS): δ 1.40–1.49 (m, 1H, H-6**a**), 1.57–1.80 (m, 2.5 H, H-6**a**, H-5**a**, CH_2-7**b**), 1.95 (dt, 1H, ^2J=18 Hz, ^3J=6.0 Hz, H-5**a**), 2.20 (dd, 0.25H, ^2J=16.5 Hz, ^3J=5.6 Hz, H-5**b**), 2.28 (m, 0.25H, CH-8**b**), 2.52 (dd, 0.25H, ^2J=16.5 Hz, ^3J=9.0 Hz, H-5**b**), 2.73 (dt, 0.25H, ^2J=19.0 Hz, ^3J=5.2 Hz, H-8**b**), 3.00 (dd, 1H, ^2J=18.5 Hz, ^3J=6.2 Hz, H-8**a**), 3.10 (dd, 1H, ^2J=18.5 Hz, ^3J=7.4 Hz, H-8**a**), 3.73–3.93 (m, 1.25H, H-7**a**, H-6**b**), 4.64 (d, 1H, ^2J=14.4 Hz, CH_2–N**a**), 4.66 (d, 0.25H, ^2J=14.2 Hz, CH_2–N **b**), 4.81 (d, 0.25H, ^2J=14.2 Hz, CH_2–N **b**), 4.85 (d, 1H, ^2J=14.4 Hz, CH_2–N), 5.17 (d, 0.25H, ^3J=7.0 Hz, H-4**b**), 5.19 (d, 1H, ^3J=7.0 Hz, H-4**a**), 6.38 (d, 1H, ^3J=7.0 Hz, H-3**a**), 6.40 (d, 0.25H, ^3J=7.0 Hz, H-3**b**), 7.00–7.13 (m, 6.25H, H–Ph **a**+**b**); ^{13}C NMR: **15a**: δ 26.4 (CH_2), 26.8 (CH_2), 28.2 (CH_2), 52.4 (CH_2), 80.6 (CH), 107 (CH), 123.2 (C), 127.9 (CH), 128.0 (CH), 129.3 (CH), 134.4 (CH), 136.3 (C), 145.4 (C), 161.9 (CO); **15b**: δ 22.3 (CH_2), 27.1 (CH_2), 32.7 (CH_2), 52.4 (CH_2), 80.2 (CH), 107.0 (CH), 127.9 (CH), 128.0 (CH), 129.3 (CH), 125.9 (C), 134.6 (CH), 136.3 (C), 142.5 (C), 161.9 (CO); MS [*m*/*z* (%)]: EI: 284 (26, $M^{+\cdot}$), 237 (66, $M^{+\cdot}-HNO_2$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{12}H_{16}N_2O_3$: 284.1161; found: 284.1162.

4.5.7. 2-Benzyl-5,6,7,8-tetrahydro-1(2*H*)-isoquinolinone 16. A solution of 0.2 g sulfolene pyridinone in *o*-dichlorobenzene (20 mL) was transferred to a steel vessel. The vessel was loaded with ethene (40 atm) and heated at 160°C for 48 h. After cooling the solvent was evaporated (Kugelrohr) and the residue was purified by column chromatography (silica, 10 EtOAc/90 CH_2Cl_2). Yield: 22%; white powder; mp: 110°C (CH_2Cl_2/hexane); IR (KBr/cm^{-1}): 2936, 1647, 1593; ^{1}H NMR: δ 1.70–1.76 (m, 4H, H-6+H-7), 2.51 (t, 2H, *J*=5.8 Hz, H-5 of H-8), 2.56 (t, 2H, *J*=5.8 Hz, H-8 of H-5), 5.11 (s, 2H, CH_2–N), 5.90 (d, 1H, *J*=7.0 Hz, H-4), 7.03 (d, 1H, *J*=7.0 Hz, H-3), 7.26–7.34 (m, 5H, H–Ph); ^{13}C NMR: δ 21.9 (CH_2), 22.2 (CH_2), 23.7 (CH_2), 29.2 (CH_2), 51.8 (CH_2–N), 108.3 (C-4), 127.7 (C-8a), 127.8, 1281, 128.7, 132.5 (C-3), 136.9 (C-*ipso*), 146.9 (C-4a), 162.5 (C-1); MS [*m*/*z* (%)]: EI: 239 (100, $M^{+\cdot}$), 148 (100, $M^{+\cdot}-C_7H_7$), 91 (90, $C_7H_7^+$); HRMS: calcd for $C_{16}H_{17}NO$: 239.1310; found: 239.1309.

4.5.8. 2-Benzyl-6-[(4-methylphenyl)sulfonyl][2,7]-naphthyridin-1(2*H*)-one 18. Dienophile: 5 equiv. of *p*-toluenesulfonylcyanide. Yield: 69%; yellow crystals; mp: 168–169°C (CH_2Cl_2/hexane); IR (KBr/cm^{-1}): 3061, 1652, 1619, 1317, 1124; ^{1}H NMR: δ 2.40 (s, 3H, CH_3), 5.19 (s, 2H, CH_2–N), 6.54 (d, 1H, *J*=7.4 Hz, H-4), 7.26–7.33 (m, 9H, H–Ph), 7.40 (d, 1H, *J*=7.4 Hz, H-3), 8.24 (s, 1H, H-5), 9.57 (s, 1H, H-8); ^{13}C NMR: δ 21.6 (CH_3), 51.9 (CH_2–N), 104.4 (C-4), 117.9 (C-5), 122.3 (C-8a), 128.1, 128.3, 128.9, 129.1, 129.8, 135.4, 135.6, 138.1 (C-3), 143.7 (C-4a), 145.1 (C-*ipso*), 152.6 (C-8), 159.9 (C-6), 160.6 (C-1); MS [*m*/*z* (%)]: EI: 390 ($M^{+\cdot}$), 326 (48, M^+-SO_2), 235 (27, $M^{+\cdot}-SO_2Tol$), 91 (100, Bn^+); HRMS: calcd for $C_{22}H_{18}N_2O_3S$: 390.1038; found: 390.1030; CHN analysis: calcd for $C_{22}H_{18}N_2O_3S$: C 67.67, H 4.65, N 7.17; found: C 67.38, H 4.61, N 7.04.

4.5.9. *N*-[(1-Benzyl-4-methyl-2-oxo-2*H*-pyridin-3-yl)methyl]-4-methylbenzenesulfonamide 19. Yield: 53%; pale yellow crystals; mp 108–110°C; ^{1}H NMR: δ 2.17 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.07 (d, 2H, ^3J=6.6 Hz, CH_2), 4.98 (s, 2H, CH_2–N), 5.90 (d, 1H, ^3J=7.1 Hz, H-4), 6.16 (t broad, 1H, ^3J=6.6 Hz, NH), 7.04 (d, 1H, ^3J=7.1 Hz, H-3), 7.07 (d, 2H, ^3J=8.5 Hz, H–Ph), 7.22–7.33 (m, 5H, H–Ph),

7.63 (d, 2H, ^3J=8.5 Hz, H–Ph); ^{13}C NMR: 19.0 (CH_3), 21.4 (CH_3), 40.8 (CH_2), 51.9 (CH_2), 109.8 (CH), 124.3, 126.7 (CH), 128.0 (CH), 128.1 (CH), 128.8 (CH), 129.2 (CH), 134.8, 135.9, 137.5, 142.8 (CH), 147.9, 161.9; MS [*m/z* (%)]: EI: 382 (2, $M^{+\cdot}$), 227 (100, $M^{+\cdot}-SO_2C_7H_7$), 155 (2, $SO_2C_7H_7$), 91 (86, $C_7H_7^+$); HRMS: calcd for $C_{21}H_{22}N_2O_3S$: 382.1351; found: 382.1352.

4.6. General procedure for substitution of sulfolene pyridinone in position 1

To a solution of sulfolene pyridinone (0.2 g or 0.7 mmol) in 20 mL dry THF were added dropwise 1.2 equiv. tetrabutylammonium-fluoride at rt. After stirring for 20 min 1–3 equiv. of an electrophile were added. After a few hours NH_4Cl-solution (20 mL) was added, and stirring was continued for 15 min. The mixture was extracted with CH_2Cl_2 (3×10 mL), the organic phases were dried over $MgSO_4$ and the solvent evaporated. The residue was purified by column chromatography (alumina; 15% EtOAc/85% CH_2Cl_2).

4.6.1. 5-Benzyl-1,3-dihydro-1-methyl-2,2-dioxothieno[3,4-*c*]pyridin-4(5*H*)-one 20. Yield: 70%; white crystals, mp: 156°C (CH_2Cl_2/hexane); IR (KBr/cm^{-1}): 3065, 1653; ^{1}H NMR: δ 1.59 (d, 3H, ^3J=7.2 Hz, CH_3), 4.20 (m, 3H, H-1+H-3), 5.14 (s, 2H, CH_2–N), 6.11 (d, 1H, *J*=7.2 Hz, H-7), 7.35 (d, 1H, ^3J=7.2 Hz, H-6), 7.33 (m, 5H, H–Ph); ^{13}C NMR: δ 123 (CH_3), 52.2 (CH_2–N), 53.3 (C-3), 62.2 (C-1), 102.3 (C-7), 121.3 (C-3a), 128.2 (C-arom), 128.4 (C-arom), 129.0 (C-arom), 135.5 (C-*ipso*), 138.2 (C-6), 148.0 (C-7a), 158.7 (C-4); MS [*m/z* (%)]: CI: 290 (100, MH^+), 226 (39, MH^+-SO_2).

4.6.2. 1,5-Dibenzyl-1,3-dihydro-2,2-dioxothieno[3,4-c]pyridin-4(5*H*)-one 21. Yield: 70%; colourless oil; IR (NaCl/cm^{-1}): 3083, 1650; ^{1}H NMR: δ 3.02 (dd, 1H, ^2J=15 Hz, ^3J=6 Hz, CH_2–Ph), 3.55 (dd, 1H, ^2J=15 Hz, ^3J=9 Hz, CH_2–Ph), 4.08 (d, 1H, ^2J=16 Hz, H-3), 4.24 (d, 1H, ^2J=16 Hz, H-3), 4.37 (dd, 1H, ^3J=9 Hz, ^3J=6 Hz, H-1), 5.10 (2×d, 2H, ^2J=14.5 Hz, CH_2–N), 5.67 (d, 1H, ^3J=7 Hz, H-7), 7.20 (d, 1H, ^3J=7 Hz, H-6), 7.30–7.38 (m, 5H, H–Ph); ^{13}C NMR: δ 35.1 (C-1′), 52.28 (C-Bn), 53.40 (C-3), 67.9 (C-1), 10.3.4 (C-7), 121.9 (C-3a), 127.5 (C-arom), 1282 (C-arom), 128.4 (C-arom), 128.8 (C-arom), 129.0 (C-arom), 129.3 (C-arom), 135.2 (C-*ipso*), 135.4 (C-*ipso*), 137.5 (C-6), 147.0 (C-7a), 158.7 (C-4); MS [*m/z* (%)]: EI: 365 (9, $M^{+\cdot}$), 301 (36, $M^{+\cdot}-SO_2$), 210 (15, $M^{+\cdot}-SO_2$, $-C_7H_7$); HRMS: calcd for $C_{21}H_{19}NO_3S$: 365.1086; found: 365.1090.

4.6.3. 5-Benzyl-1,3-dihydro-1-(4-pentenyl)-2,2-dioxothieno[3,4-c]pyridin-4(5*H*)-one 22. Yield: 56%; colourless oil; IR (NaCl/cm^{-1}): 2930, 1650, 1310, 1195; ^{1}H NMR: δ 1.72 (m, 2H, H-2′), 1.89 (m, 1H, H-1′), 2.07 (m, 1H, H-1′), 2.14 (m, 2H, H-3′), 4.09 (dd, 1H, ^3J=9 Hz, ^3J=5 Hz, H-1), 4.20 (m, 2H, H-3), 5.01 (m, 2H, H-5′), 5.13 (s, 2H, CH_2–N), 5.77 (ddt, 1H, $^{trans}J$=17 Hz, ^{cis}J=10 Hz, ^3J=7 Hz, H-4′), 6.11 (d, 1H, ^3J=7 Hz, H-7), 7.29 (d, 1H, ^3J=7 Hz, H-6), 7.34 (m, 5H, H–Ph); ^{13}C NMR: δ 25.5 (C-2′), 28.0 (C-1′), 33.1 (C-3′), 52.2 (CH_2–N), 53.7 (C-3), 66.9 (C-1), 102.7 (C-7), 115.6 (C-5′), 121.5 (C-3a), 128.2 (C-arom), 128.3 (C-arom), 128.9 (C-arom), 135.4 (C-*ipso*), 137.2 (C-4′), 137.9 (C-6), 147.2 (C-7a), 158.6 (C-4); MS [*m/z* (%)]: EI: 343 (17, $M^{+\cdot}$), 279 (32, $M^{+\cdot}-SO_2$), 188 (48, $M^{+\cdot}-SO_2-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{19}H_{21}NO_3S$: 343.1242; found: 343.1241.

4.6.4. *N*-Allyl-2-(5-benzyl-1,3-dihydro-2,2,4-trioxo-5*H*-thieno[3,4-*c*]pyridin-1-yl)-*N*-methylacetamide 24. Yield: 63%; yellow oil; IR (NaCl/cm^{-1}): 3082, 2925, 1652, 1595, 1309, 1153; two rotamers: ^{1}H NMR: δ 2.69 and *2.70* (dd, 1H, ^2J=16 Hz, ^3J=8 Hz, H-1′), 2.97 and *2.99* (s, 3H, CH_3), 3.19 and *3.24* (dd, 1H, ^2J=16 Hz, ^3J=5 Hz, H-1′), 3.91 and *4.02* (ddt, ^2J=17 Hz, ^3J=6 Hz, ^4J=1.5 Hz, H-4′), 4.25 and *4.26* (2×d, 1H, ^2J=16 Hz, H-3), 4.88 (dd, 1H, ^3J=8 Hz, ^3J=5 Hz, H-1), 5.14 (2×d, 2H, ^2J=14.4 Hz, CH_2–N), 5.17 (d, 1H, $^{trans}J$=14 Hz, H-6′), 5.22 (^{cis}J=4 Hz, ^4J=1.5 Hz, H-6′), 5.76 (m, 1H, H-5′), 6.24 and *6.27* (s, 1H, ^3J=7 Hz, H-7), 7.30–7.38 (m, 6H, H-6+H–Ph); ^{13}C NMR: δ 32.6 and *33.6* (C-1′), 34.2 and *34.6* (CH_3), 50.5 and *52.0* (C-4′), 52.3 (CH_2–N),53.8 (C-3), 63.5 (C-1), 103.3 and *103.4* (C-7), 117.0 and *117.8* (C-6′), 121.6 (C-3a), 128.3 (C-arom), 128.33 (C-arom), 128.4 (C-arom), 128.8 (C-arom), 129.0 (C-arom), 131.7 and *132.3* (C-5′), 135.5 (C-*ipso*), 137.9 (C-6), 147.3 and *147.4* (C-7a), 158.6 (C-4), 167.7 and *168.0* (C-2′); MS [*m/z* (%)]: EI: 386 (5, $M^{+\cdot}$), 322 (24, $M^{+\cdot}-SO_2$); HRMS: calcd for $C_{20}H_{22}N_2O_4S$: 386.1300; found: 396.1306.

4.7. General procedure for substitution of sulfolene pyridinone in position 3

To a solution of 0.2 g (0.7 mmol) of the precursor in dry THF (25 mL) under argon atmosphere was added dropwise at −78°C 2.1 equiv. of a solution of butyllithium (1 M in THF). After stirring at −78°C for 20 min, 1.1 equiv. electrophile was added. The reaction mixture was stirred for another hour at −78°C and was then allowed to warm up to rt. Then a solution of NH_4Cl (5 mL) was added carefully, the mixture was extracted with CH_2Cl_2 (3×10 mL), the combined organic phases were dried ($MgSO_4$) and evaporated to give a residue that was purified by column chromatography (alumina;15% EtOAc/85% CH_2Cl_2).

4.7.1. 3,5-Dibenzyl-1,3-dihydro-2,2-dioxothieno[3,4-*c*]pyridin-4(5*H*)-one 26. Yield: (60%); white crystals, mp: 182–182.5°C; IR (KBr/cm^{-1}): 3082, 1641; ^{1}H NMR: δ 3.45 (dd, 1H, ^2J=15 Hz, ^3J=7 Hz, 3-CH_2–Ph), 3.55 (d, 1H, ^2J=16 Hz, H-1), 3.58 (dd, 1H, ^2J=15 Hz, ^3J=2.5 Hz, 3-CH_2–Ph), 3.88 (d, 1H, ^2J=16 Hz, H-1), 4.56 (dd, 1H, ^3J=7 Hz, ^3J=2.5 Hz, H-3), 5.07 (d, 1H, ^2J=14.5 Hz, CH_2–N), 5.27 (d, 1H, ^2J=14.5 Hz, CH_2–N), 5.94 (d, 1H, ^3J=7 Hz, H-7), 7.13 (m, 2H, H–Ph), 7.30 (m, 3H, H–Ph), 7.30 (s, 1H, ^3J=7 Hz, H-6), 7.37 (m, 5H, H–Ph); ^{13}C NMR: δ 33.61 (C-3′), 52.3 (CH_2–N), 56.9 (C-1), 66.3 (C-3), 103.9 (C-7), 126.5 (C-3a), 126.9 (C-arom), 128.0 (C-arom), 128.1 (C-arom), 128.4 (C-arom), 129.0 (C-arom), 130.1 (C-arom), 135.7 (C-*ipso*), 137.9 (C-6), 142.6 (C-7a), 158.7 (C-4); MS [*m/z* (%)]: CI: 365 (0, $M^{+\cdot}$), 301 (70, $M^{+\cdot}-SO_2$), 210 (74, $M^{+\cdot}-SO_2$, $-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{21}H_{19}NO_3S$: 365.1086; found: 365.1081.

4.7.2. 5-Benzyl-1,3-dihydro-3-(4-pentenyl)-2,2-dioxothieno[3,4-*c*]pyridin-4(5*H*)-one 27. Yield: 60%; white crystals, mp: 90.5–91.3 (CH_2Cl_2/hexane); IR (KBr/cm^{-1}):

2928, 1654, 1313, 1187; ^{1}H NMR: δ 1.67 (m, 2H, H-3′), 2.10 (m, 4H, H-1′+H-2′), 4.14 (2×d, 2H, ^2J=16.6 Hz, H-1), 4.28 (dd, 1H, ^3J=8 Hz, ^3J=4 Hz, H-3), 4.79 (dt, 1H, ^{cis}J=10 Hz, ^4J=1 Hz, H-5′), 4.96 (m, 1H, H-5′), 5.10 (2×d, 2H, ^2J=14.5 Hz, H-N), 5.79 (ddt, 1H, $^{trans}J$=17 Hz, ^{cis}J=10 Hz, ^3J=6 Hz, H-4′), 6.10 (d, 1H, ^3J=7 Hz, H-7), 7.32 (d, 1H, ^3J=7 Hz, H-6), 7.30–7.35 (m, 5H, H–Ph); ^{13}C NMR: δ 25.9 (C-1′), 28.5 (C-2′), 33.5 (C3′), 52.3 (CH_2–N), 56.8 (C-1), 65.3 (C-3), 103.3 (C-7), 115.9 (C-5′), 127.2 (C-3a), 128.2 (C-arom), 128.4 (C-arom), 129.1 (C-arom), 135.6 (C-*ipso*), 137.8 (C-6), 137.9 (C4′), 141.7 (C-7a), 158.7 (C-4); MS [*m*/*z* (%)]: EI: 343 (5, $M^{+\cdot}$), 279 (16, $M^{+\cdot}-SO_2$), 175 (15, $M^{+\cdot}-C_5H_9$), 188 (15, $M^{+\cdot}-SO_2$, $-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{19}H_{21}NO_3S$: 343.1242; found: 343.1239.

4.7.3. 5-(5-Benzyl-1,3-dihydro-2,2,4-trioxo-5*H*-thieno[3,4-*c*]pyridin-3-yl) pentanenitrile 28. Yield: 58%; yellow oil; IR (NaCl/cm^{-1}): 3061, 2933, 1651, 1599, 1311, 1117; ^{1}H NMR: δ 1.70–17.4 (m, 4H, H-2′+H-3′), 2.05–2.20 (m, 2H, H-1′), 3.36 (t, 2H, ^3J=7 Hz, H-4′), 4.16 (2×d, 2H, ^2J=16.6 Hz, H-1), 4.23 (dd, 1H, ^3J=7.3 Hz, ^3J=4 Hz, H-3), 5.20 (2×d, 2H, ^2J=14.6 Hz, CH_2–N), 6.11 (d, 1H, ^3J=7 Hz, H-7), 7.26 (d, 1H, ^3J=7 Hz, H-6), 7.29–7.35 (m, 5H, H–Ph); ^{13}C NMR: δ 16.7 (C-4′), 25.1 (C-3′), 25.7 (c-2′), 27.8 (C-1′), 52.4 (CH_2–N), 56.8 (C-1), 64.8 (C-3), 103.3 (C-7), 119.4 (CN), 126.5 (C-3a), 128.2 (C-arom), 128.4 (C-arom), 129.1 (C-arom), 135.4 (C-*ipso*), 138.2 (C-6), 141.9 (C-7a), 158.7 (C-4); MS [*m*/*z* (%)]: EI: 356 (6, $M^{+\cdot}$), 316 (4, $M^{+\cdot}-C_2H_2N$), 292 (12, $M^{+\cdot}-SO_2$), 275 (10, $M^{+\cdot}-C_5H_8N$), 252 (28, $M^{+\cdot}-C_2H_2N$, $-SO_2$), 224 (50, $M^{+\cdot}-C_4H_6N$, $-SO_2$), 201 (8, $M^{+\cdot}-SO_2$, $-C_7H_7^+$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{19}H_{20}N_2O_3S$: 356.1195; found 356.1193.

4.7.4. 4-(5-Benzyl-1,3-dihydro-2,2,4-trioxo-5*H*-thieno[3,4-*c*]pyridin-3-yl)butanenitrile 29. Yield: 44%; yellow crystals, mp 121–122°C; IR (KBr/cm^{-1}): 3062, 2928, 2245, 1647; ^{1}H NMR: δ 1.95 (m, 2H, H-2′), 2.20 (m, 2H, H-1′), 2.43 (t, 2H, ^3J=8 Hz, H-3′), 4.18 (2×d, 2H, ^2J=16.6 Hz, H-1), 4.25 (dd, 1H, ^3J=12.1 Hz, ^3J=7.3 Hz, H-3), 5.14 (2×d, 2H, ^2J=15.4 Hz, CH_2–N), 6.14 (d, 1H, ^3J=7 Hz, H-7), 7.28 (d, 1H, ^3J=7 Hz, H-6), 7.33 (m, 5H, H–Ph); ^{13}C NMR: δ 17.0 (C-3′), 22.8 (C-2′), 28.2 (C-1′), 52.4 (CH_2–N), 56.6 (C-1), 64.8 (C-3), 103.3 (C-7), 118.5 (CN), 126.2 (C-3a), 128.2 (C-arom), 128.5 (C-arom), 129.1 (C-arom), 138.3 (C-6), 142.1 (C-7a), 158.7 (C-4); MS [*m*/*z* (%)]: EI: 342 (5, $M^{+\cdot}$), 278 (15, $M^{+\cdot}-SO_2$), 224 (51, $M^{+\cdot}-SO_2$, $-C_3H_4N$), 187 (12, $M^{+\cdot}-SO_2$, $-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{18}H_{18}N_2O_3S$: 342.1038; found: 342.1035.

4.7.5. Methyl 5-benzyl-1,3-dihydro-2,2,4-trioxo-5*H*-thieno[3,4-*c*]pyridin-3-carboxylate 30. Yield: 55%; yellow oil; IR (NaCl/cm^{-1}): 3065, 2926, 1746, 1649, 1319, 1110; ^{1}H NMR: δ 3.85 (s, 3H, CH_3), 4.23 (d, 2H, ^2J=16 Hz, H-1), 4.35 (s, 1H, H-3), 5.16 (2×d, 2H, ^2J=14 Hz, CH_2–N), 6.19 (d, 1H, ^3J=7 Hz, H-7), 7.26–7.32 (m, 6H, H-6+H–Ph); ^{13}C NMR: δ 52.3 (CH_2–N), 54.9 (CH_3), 58.3 (C-1), 71.2 (C-3), 103.0 (C-7), 121.8 (C-3a), 128.3 (C-arom), 128.8 (C-arom), 129.8 (C-arom), 136.3 (C-*ipso*), 138.1 (C-6), 143.1 (C-7a), 158.5 (C-4), 169.2 (CO); MS [*m*/*z* (%)]: EI: 333 (9, $M^{+\cdot}$), 269 (15, $M^{+\cdot}-SO_2$), 237 (10, $M^{+\cdot}-SO_2$, $-CH_3OH$), 211 (24, $M^{+\cdot}-SO_2$, $-CO_2Me$), 178 (10, $M^{+\cdot}-SO_2$, $-CH_3OH$, $-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{16}H_{15}NO_5S$: 333.0671; found: 333.0667.

4.7.6. *N*,*N*-Diallyl-5-benzyl-1,3-dihydro-2,2,4-trioxo-5*H*-thieno[3,4-*c*]pyridin-3-carboxamide 34. Yield: 58%; yellow oil; IR (NaCl/cm^{-1}): 3080, 1658, 1590, 1310, 1150; ^{1}H NMR: δ 4.02–4.11 (m, 2H, CH_2NCO), 4.13 (d, 1H, ^2J=16 Hz, H-1), 4.22–4.30 (m, 1H, CH_2NCO), 4.48 (ddt, 1H, ^2J=18 Hz, ^3J=5 Hz, ^4J=1 Hz, CH_2NCO), 4.65 (d, 1H, ^2J=16 Hz, H-1), 4.99 (d, 1H, ^2J=15 Hz, CH_2–N), 5.15–5.27 (m, 2H, =CH_2), 5.26 (d, 1H, ^2J=15 Hz, CH_2–N), 5.30 (s, 1H, H-3), 5.38 (dm, 1H, ^{cis}J=10 Hz, =CH_2), 5.46 (dm, 1H, $^{trans}J$=17 Hz, =CH_2), 5.70–5.84 (m, 1H, H–C=), 5.92–6.08 (m, 1H, H–C=), 7.26 (d, 1H, ^3J=7.2 Hz, H-7), 7.29–7.40 (m, 6, H-6+H–Ph); ^{13}C NMR: δ 49.1 (C-3′), 49.7 (C-3′), 52.4 (CH_2–N), 58.3 (C-1), 66.5 (C-3), 103.7 (C-7), 117.8 (C-5′), 117.7 (C-5′), 125.5 (C-3a), 128.1 (C-arom), 128.4 (C-arom), 129.1 (C-arom), 131.1 (C-4′), 131.7 (C-4′), 135.2 (C-*ipso*), 138.9 (C-6), 144.7 (C-7a), 164.1 (C-4), 177.8 (C-1′); MS [*m*/*z* (%)]: EI: 398 (2, $M^{+\cdot}$), 334 (15, $M^{+\cdot}-SO_2$), 293 (3, $M^{+\cdot}-SO_2$, $-C_3H_5$), 239 (16, $M^{+\cdot}-SO_2$, $-C_6H_{11}N$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{21}H_{22}N_2O_4S$: 398.1300; found: 398.1298.

4.7.7. (*E*)-*N*-Allyl-3-(1-benzyl-4-methyl-2-oxo-1*H*-pyridin-3-yl)-*N*-methylpropene amide 35. Yield: 50%; yellow oil; IR (NaCl/cm^{-1}): 3079, 2929, 1653, 1596; two rotamers: ^{1}H NMR: δ 2.37 and *2.38* (s, 3H, CH_3), 3.03 and *3.08* (s, 3H, CH_3–N), 4.1 (m, 2H, H-5′), 5.17 (m, 4H, CH_2–N+H-7′), 5.81 (m, 1H, H-6′), 6.08 and *6.10* (d, 1H, ^3J=7 Hz, H-5), 7.15 and *7.19*(d, 1H, ^3J=7 Hz, H-6), 7.30 (m, 5H, H–Ph), 7.77 and *7.79* (d, $^{trans}J$=15 Hz, H-2′), 8.03 and *8.12* (d, 1H, $^{trans}J$=15 Hz, H-1′); ^{13}C NMR: δ 20.12 (CH_3-4), 50.4 and *51.9* (C-5′), 52.3 and *51.8* (CH_2–N), 110.0 and *110.1* (C-5), 116.9 (C-7′), 121.1 (C-2′), 122.8 (C-3), 127.8 (C-arom), 127.9 (C-arom), 128.9 (C-arom), 133.1 (C-6′), 134.6 and *134.7* (C-6), 135.7 and *135.8* (C-1′), 136.2 (C-*ipso*), 151.3 (C-4), 161.0 (C-2), 167.7 and *168.3* (C-3′); MS [*m*/*z* (%)]: EI: 224 (50, $M^{+\cdot}$), 133 (10, $M^{+\cdot}-C_7H_7$), 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{20}H_{22}N_2O_2$: 322.1681; found: 322.1681.

4.8. General procedure for intramolecular Diels–Alder reactions

A solution of 100 mg of a substituted sulfolene pyridinone in 20 mL *o*-dichlorobenzene was thermolysed at 150°C for 4–8 h under an inert atmosphere (N_2 of Ar). The solvent was removed by Kugelrohr distillation and the residue was purified by column chromatography (silica; 15% EtOAc/85% CH_2Cl_2) to give following compounds.

4.8.1. 3-Benzyl-6,6a,7,8,9,9a-hexahydro-5*H*-cyclopenta-(*f*(-isoquinolin-4(3*H*)-one 36, 37. Yield: 67%; colourless oil; IR (NaCl/cm^{-1}): 3065, 2927, 1644; ^{1}H NMR: δ 1.60–2.70 (m, 12H, CH_2+CH), 5.10 (2×d, 1H, ^2J=14.5 Hz, CH_2–N), 5.12 (s, 1H, CH_2–N), 5.98 (d, 0.46H, ^3J=7.0 Hz, H-1), 6.02 (d, 0.54H, ^3J=7.0 Hz, H-1), 7.05 (d, 0.46H, ^3J=7.0 Hz, H-2), 7.09 (d, 0.54H, ^3J=7.0 Hz, H-2), 7.26–7.34 (m, 5H, H–Ph); ^{13}C NMR: δ 22.6 (CH_2), 22.7 (CH_2), 23.9 (CH_2), 25.8 (CH_2), 27.2 (CH_2), 27.5 (CH_2), 30.3 (CH_2),

31.6 (CH_2), 32.9 (CH_2), 36.6 (CH), 42.7 (CH), 43.2 (CH), 41.1 (CH), 51.8 (CH_2–N), 51.9 (CH_2–N), 105.7 (C-1), 108.1 (C-1), 127.1 (C-4a), 127.7 (C-arom), 128.2 (C-arom), 128.7 (C-arom), 132.8 (C-2), 133.1 (C-2), 150.3 (C-9b), 150.4 (C-9b), 162.3 (C-4); MS [*m*/*z* (%)]: EI: 279 (89, $M^{+\cdot}$), 238 (10, $M^{+\cdot}-C_3H_5$), 188 (100, $M^{+\cdot}-C_7H_7$), 91 (99; $C_7H_7^+$); HRMS: calcd for $C_{19}H_{21}NO$: 279.1623; found: 279.1620.

4.8.2. (4a*S* *,10b*S* *)-8-Benzyl-1,2,3,4,4a,5,6,10b-octahydro-3-methyl-[3,8]phenanthroline-2,7(8*H*)-dione 38 and (4a*S* *,10b*R* *)-8-benzyl-1,2,3,4,4a,5,6,10b-octahydro-3-methyl-[3,8]phenanthroline-2,7(8*H*)-dione 39. Yield: 83%; colourless oil; IR (NaCl/cm^{-1}): 3067, 2925, 1644, 1545; ^{1}H NMR: δ 1.43 (ddd, 0.3H, ^2J=18 Hz, ^3J=12 Hz, ^3J=6 Hz, H-5 **39**), 1.77–1.88 (m, 2H, H-5a **39**+H-5 **38**), 2.00 (m, 0.3H, H-5 **39**), 2.20 (m, 1.7H, H-5a **38**+H-1 **39**), 2.33 (dd, 0.7H, ^2J=17.5 Hz, ^3J=11 Hz, H-1 **38**), 2.44–2.50 (m, 0.6H, H-6 **39**), 2.53 (ddd, 0.7H, ^2J=19 Hz, ^3J=10 Hz, ^3J=8 Hz, H-6 **38**), 2.65 (dd+m, 1H, ^2J=17.5 Hz, ^3J=6.5 Hz, H-1 **38**+H-10b **39**), 2.85 (ddd, 0.7H, ^2J=19 Hz, ^3J=6 Hz, ^3J=3 Hz, H-6 **38**), 2.88–2.98 (m, 0.7H, H-10b **38**), 2.95 (s, 2.1H, CH_3 **38**), 2.98 (s, 0.9H, CH_3 **39**), 3.12 (t, 0.3, ^2J=^3J=12 Hz, H-4 **39**), 3.17 (dd, 0.7H, ^2J=12.5 Hz, ^3J=3 Hz, H-4 **38**), 3.35 (dd, 0.3H, ^2J=12 Hz, ^3J=5 Hz, H-4 **39**), 3.62 (dd, 0.7H, ^2J=12.5 Hz, ^3J=5.5 Hz, H-4 **38**), 5.11 (2×d, 2H, ^2J=14.5 Hz, CH_2–N **38**+**39**), 5.92 (d, 0.3H, ^3J=7 Hz, H-10 **38**), 6.02 (d, 0.7H, ^3J=7 Hz, H-10 **39**), 7.12 (d, 0.3H, ^3J=7 Hz, H-9 **38**), 7.15 (d, 0.3H, ^3J=7 Hz, H-9 **39**), 7.25–7.33 (m, 5H, H–Ph **38**+**39**): ^{13}C NMR: δ 22.6 (C-5 **38**), 23.6 (C-5 **39**), 23.4 (C-6 **38**), 25.3 (C-6 **39**), 30.9 (C-4a **38**), 34.4 (CH_3 **39**), 34.7 (CH_3 **38**), 35.2 (C-10b **38**), 35.4 (C-1 **38**), 35.5 (C-4a **39**), 36.7 (C-1 **39**), 37.9 (C-10b **39**), 52.0 (CH_2–N **38**+**39**), 104.0 (C-10 **39**), 106.4 (C-10 **38**), 126.1 (C-6a **39**), 127.3 (C-6a **38**), 127.9 (C-arom **38**+**39**), 128.2 (C-arom **38**+**39**), 128.8 (C-arom **38**+**39**), 133.8 (C-9 **38**+**39**), 136.5 (C-*ipso* **38**+**39**), 146.5 (C-10a **39**), 148.2 (C-10a **38**), 162.0 (C-7 **39**), 162.3 (C-7 **38**), 167.9 (C-2 **39**), 168.7 (C-2 **38**); MS [*m*/*z* (%)]: EI: 322 (63, $M^{+\cdot}$), 231 (20, $M^{+\cdot}-C_7H_7$), 203 (5, $M^{+\cdot}-C_7H_7$, –CO), 188, $M^{+\cdot}-C_7H_7$, –CO), 188 (15, $M^{+\cdot}-C_7H_7$, –NHCO), 91 (100; $C_7H_7^+$); HRMS: calcd for $C_{20}H_{22}N_2O_2$: 322.1681; found: 322.1679.

4.8.3. (6a*R* *,9a*R* *)-2-Benzyl-6,6a,7,8,9,9a-hexahydro-5*H*-cyclopenta[*h*]isoquinolin-1(2*H*)-one 40. Two conformers. Yield: 60%; colourless oil; IR (NaCl/cm^{-1}): 3030, 2935, 1650; ^{1}H NMR: δ 1.20–1.55 (m, 4H, 3×H+H-6a **B**), 1.60–1.72 (m, 3H), 1.99–2.04 (m, 1H, H–(CH_2-**B**)), 2.10–2.19 (m, 1H, H-6a **A**), 2.20–2.29 (m, 1H, H-9a **B**), 2.43–2.49 (m, 2H, CH_2 **A**), 2.60–2.80 (m, 2H, CH_2 **B**) 2.80–2.88 (m, 1H, H-(CH_2 **B**)), 3.01–3.08 (m, 1H, H-9a **A**), 4.92 (d, 1H, ^2J=14.5 Hz, CH_2–N **B**), 4.96 (d, 1H, ^2J=14.5 Hz, CH_2–N **A**), 5.24 (d, 1H, ^2J=14.5 Hz, H-Bn **B**), 5.25 (d, 1H, ^2J=14.5 Hz, H-Bn **A**), 5.91 (d, 1H, ^3J=7.0 Hz, H-4 **A**+**B**), 7.02 (dd, 1H, ^3J=7.0 Hz, ^6J=1 Hz, H-3 **A**+**B**), 7.25–7.32 (m, 5H, H–Ph **A**+**B**); ^{13}C NMR: δ 22.4 (CH_2 **B**), 26.8 (CH_2 **B**), 29.3 (CH_2 **B**), 29.6 (CH_2 **B**), 31.6 (CH_2 **B**), 2×44.8 (CH **B**), 23.6 (CH_2 **A**), 25.5 (CH_2 **A**), 29.0 (CH_2 **A**), 31.4 (CH_2 **A**), 31.7 (CH_2 **A**), 37.1 (CH **A**), 38.7 (CH **A**), 51.6 (CH_2–N **B**), 51.8 (CH_2–N **A**), 108.0 (C-4 **A**+**B**), 127.9 (C-arom **A**+**B**), 128.1 (C-arom **A**+**B**), 128.7 (C-arom **A**+**B**), 130.8 (C-9b **A**+**B**), 132.6 (C-3 **A**), 133.2 (C-3 **B**) 137.0 (C-*ipso* **A**+**B**) 148.1 (C-4a **A**+**B**), 162.3 (C-1 **A**+**B**); MS [*m*/*z* (%)]: EI: 279 (100, $M^{+\cdot}$), 188 (52, $M^{+\cdot}-C_7H_7$), 91 (73, $C_7H_7^+$); HRMS: calcd for $C_{19}H_{21}NO$: 279.1623; found: 279.1625.

4.8.4. (3a*S* *, 9b*S* *)-2-Allyl-8-benzyl-1,3,3a,4,5,9b-hexahydro-8*H*-pyrrolol[3,4-*h*]-isoquinolin-1,9(2*H*)-dione 41. Yield: 65%; yellow crystals; mp: 156–157°C; IR (KBr/cm^{-1}): 3060, 2988, 1645, 1609; ^{1}H NMR: δ 1.65 (m, 1H, H-4), 1.80 (m, 1H, H-4), 2.47–2.53 (m, 2H, H-3a+H-5), 2.95 (d, 1H, ^2J=10 Hz, H-3), 3.65 (dd, 1H, ^2J=10 Hz, ^3J=6.0 Hz, H-3), 3.84 (dd broad, ^2J=14.9 Hz, ^3J=6.2 Hz, H-2′), 3.93 (dd broad, ^2J=14.9 Hz, ^3J=6.2 Hz, H-2′), 4.08 (d, 1H, ^3J=7.3 Hz, H-9b), 5.00 (d, 1H, ^2J=14.5 Hz, CH_2–N), 5.18 (d broad, ^{cis}J=9.9 Hz, H-2‴), 5.21 (d broad, $^{trans}J$=17 Hz, H-2‴), 5.30 (d, 1H, ^2J=14.5 Hz, CH_2–N), 5.71 (ddd, 1H, $^{trans}J$=17 Hz, ^{cis}J=9.9 Hz, ^3J=6.2 Hz, H-2″), 5.88 (d, 1H, ^3J=7 Hz, H-6), 7.06 (d, 1H, ^3J=7 Hz, H-7), 7.25–7.33 (m, 5H, H–Ph); ^{13}C NMR: δ 24.9 (C-4), 27.7 (C-5), 30.9 (C-4a), 41.6 (C-9b), 45.6 (C-2′), 50.9 (C-3), 52.0 (CH_2–N), 107.3 (C-6), 118.2 (C-2‴), 127.8 (C-arom), 128.4 (C-arom), 128.8 (C-arom), 132.8 (C-2″), 131.1 (C-9a), 134.3 (C-7), 137.0 (C-*ipso*), 147.2 (C-5a), 162.0 (C-8), 170.2 (C-1); MS [*m*/*z* (%)]: EI: 334 (40, $M^{+\cdot}$), 243 (60, $M^{+\cdot}-C_7H_7$); HRMS: calcd for $C_{21}H_{22}N_2O_2$: 334.1681; found: 334.1691.

4.8.5. (*E*)-6-(1-Benzyl-4-methyl-2-oxo-1*H*-pyridin-3-yl)-5-hexenenitrile 42. Yield: 44%; blue oil; IR (NaCl/cm^{-1}): 3032, 2935, 2245, 1648, 1594; ^{1}H NMR: δ 1.83 (q, 2H, ^3J=7 Hz, H-4′), 2.26 (3H, s, CH_3), 2.41 (m, 4H, H-3′ +H-5′), 5.41 (s, 2H, CH_2–N), 6.06 (d, 1H, ^3J=7.0 Hz, H-5), 6.44 (dt, 1H, $^{trans}J$=16.0 Hz, ^4J=1.2 Hz, H-1′), 6.83 (dt, 1H, $^{trans}J$=16.0 Hz, ^3J=7.0 Hz, H-2′), 7.10 (d, 1H, ^3J=7.0 Hz, H-6), 7.31 (m, 5H, H–Ph); ^{13}C NMR: δ 16.4 (C-5′), 20.3 (CH_3), 24.9 (C-4′), 33.0 (C-3′), 52.1 (CH_2–N), 110.0 (C-5), 119.7 (CN), 124.8 (C-3), 125.1 (C-2′), 127.8 (C-arom), 127.9 (C-arom), 128.8 (C-arom), 129.0 (C-1′), 133.6 (C-6), 136.5 (C-*ipso*), 146.1 (C-4), 161.3 (C-2); MS [*m*/*z* (%)]: EI: 292 (15, $M^{+\cdot}$), 252 (44, $M^{+\cdot}-C_2H_2N$), 224 (30, $M^{+\cdot}-C_4H_6N$), 201 (11, $M^{+\cdot}-C_7H_7$) 91 (100, $C_7H_7^+$); HRMS: calcd for $C_{12}H_{20}N_2O$: 292.1576; found:292.1575.

4.8.6. (*E*)-5-(1-Benzyl-4-methyl-2-oxo-1*H*-pyridin-3-yl)-4-pentenenitrile 43. Yield: 58%; yellow oil; IR (NaCl/cm^{-1}): 3020, 2999, 2245, 1648, 1590; ^{1}H NMR: δ 2.27 (s, 3H, CH_3), 2.50 (m, 2H, H-3′), 2.57 (m, 2H, H-4′), 5.14 (s, 2H, CH_2–N), 6.04 (d, 1H, ^3J=7.0 Hz, H-5), 6.51 (dt, 1H, $^{trans}J$=15.0 Hz, ^4J=1.3 Hz, H-1′), 6.86 (dt, 1H, $^{trans}J$=15.0 Hz, ^3J=7.0 Hz, H-2′), 7.10 (d, 1H, ^3J=7.0 Hz, H-6), 7.25–7.32 (m, 5H, H–Ph); ^{13}C NMR: δ 17.6 (C-4′), 20.3 (CH_3), 30.2 (C-3′), 52.3 (CH_2–N), 109.9 (C-5), 119.3 (CN), 124.6 (C-3), 126.1 (C-2′), 127.9 (C-arom), 127.8 (C-arom), 128.8 (C-arom), 131.4 (C-1′), 134.0 (C-6), 136.5 (C-*ipso*), 146.7 (C-4), 161.3 (C-2); MS [*m*/*z* (%)]: CI: 274 (100, MH^+).

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