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The synthesis of bicyclic 1,2,3,4-tetrahydro-1,4-benzodiazepin-5-ones from 2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide precursors

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Abstract—Sulfinylation of *o*-nitrobenzamide and subsequent hetero Diels–Alder reaction gave a series of 2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxides. The 2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxides undergo a ring opening reaction with phenyl magnesium bromide to give allylic sulfoxides, which, after [2,3]-sigmatropic rearrangement and desulfurisation, furnish unsaturated vicinal *N*-(*o*-nitrobenzoyl)-1,2-amino alcohols. Oxidation of the alcohol and reductive ring closure gave a series of bicyclic 1,2,3,4-tetrahydro-1,4-benzodiazepin-5-ones, a subset of the 'privileged' 1,4-benzodiazepine structure. A 4-hydroxy-1,2,5-benzothiadiazepin-1,1-dioxide was synthesised by the same route starting from *o*-nitrobenzenesulfonamide.

1. Introduction

The 1,4-benzodiazepine nucleus occupies a position as a 'privileged' structure within medicinal chemistry.[1] The most well-known sub-sets of this privileged set of structures are the 1,4-benzodiazepin-2-ones[2] and the 1,4-benzodiazepin-2,5-diones,[3] and these continue to attract enormous interest, due to a broad and ever evolving spectrum of biological activities.[2,3] Relatively less well studied are the 1,4-benzodiazepin-5-ones, although interest in the synthesis and biological activity even within this sub-set is considerable. Amongst the 1,4-benzodiazepin-5-ones, most attention has been paid to tricyclic systems, such as the antitumour pyrrolo-1,4-benzodiazepin-5-ones,[4] the biologically active quinazolino-fused circumdatin and asperlicin natural products,[5] the pyrido- and benzo- fused non-nucleosidic reverse transcriptase inhibitors,[6] muscarinic receptor ligands,[7] and the clinically used anti-depressant, cognition enhancing imidazolo-fused flumazenil,[8] and positron emission tomography tracers derived from flumazenil.[9] Bicyclic 1,4-benzodiazepin-5-ones have attracted attention as simplified analogues and precursors of these tricyclic systems,[10–15] are of interest generally as members of the privileged 1,4-benzodiazepine class, and are of specific interest as anti-convulsants, anti-anxiety agents, anti-depressants,[10–13] sedatives, hypnotics, muscle relaxants,[10,11] analgesics,[12] anti-tumour agents[14] and fibrinogenic receptor antagonists.[15]

Synthetic approaches to the bicyclic 1,4-benzodiazepin-5-ones most commonly involve formation of the 1,2 N–C bond as the final step. This can be achieved either via the intramolecular cyclisation of (*o*-aminobenzamido)carbonyls[11a,16a] and acetals/thioacetals,[16b] reductive cyclisation of (*o*-nitrobenzamido)carbonyls and (*o*-nitrobenzamido)-acetals/thioacetals,[14,17] intramolecular cycloadditions of (*o*-azidobenzamido)alkenes and alkynes,[8b,18] aza-Wittig ring closure of [*o*-(iminophosphoranyl)benzamido]carbonyls,[5a,19] intramolecular Michael additions of (*o*-aminobenzamido)enones,[15,20] intramolecular cyclisation of (*o*-aminobenzamido) π-allyl complexes obtained from acylnitroso-derived Diels–Alder cycloadducts,[21] or the cyclisation of α-(*o*-aminobenzamido)nitriles.[22] Construction of the 3,4 C–N bond as the final step is another common approach and can be achieved via cyclodehydrochlorination of *o*-[(2-chloroethyl)amino]benzamides,[12] cyclodehydrobromination of *o*-[(bromoalkyl)amino]aroylhydrazines,[23] and ozonolysis of *o*-(allylamino)benzamides, followed by cyclisation.[24] 1,2 or 3,4 C–N bond formation as the final step also occurs during in the reaction of anthranilamide derivatives with cyanoester epoxides[25] or bromoacetaldehyde acetals,[26] or reaction of methyl anthranilate with aziridines.[27] Other cyclisation methods include 1,7 N–C bond formation as a final step by intramolecular aromatic nucleophilic displacement,[28] 4,5 C–N formation via reduction of *N*-alkylnitrile substituted anthranilates and subsequent ring closure,[29] and 5,6 C–C bond formation via treatment of β-anilino ethylisocyanates with aluminium trichloride.[27] 1,4-Benzodiazepin-5-ones can also be made from hydride reductions of 1,4-benzodiazepin-2,5-diones,[11e,30] Schmidt reaction between the azide anion and 1,2,3,4-tetrahydroquinolin-4-ones,[31] ring expansion reactions of chloromethyl quinazolin-4-ones,[32] photolytic ring

Keywords: Benzodiazepine; 1,2-Thiazine; Reductive ring closure; Diels–Alder reaction; Sigmatropic rearrangement; Benzothiadiazepine.
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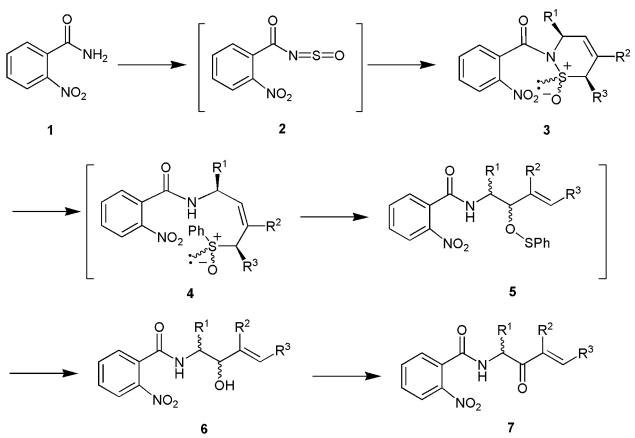
expansions of 4-azidoquinazolines,[33] and ring expansions of benzoxazines with subsequent cyclisation of the intermediate amidine carboxamides.[5b] In this paper we present a new strategy for the synthesis of the bicyclic 1,2,3,4-tetrahydro-1,4-benzodiazepin-5-one nucleus, which relies upon a novel method for the synthesis of (*o*-nitrobenzamido)carbonyl cyclisation precursors for 1,2 N–C bond formation. Reductive cyclisation of these gives the desired 1,4-benzodiazepin-5-one nucleus. The method presented in this paper is advantageous in allowing readily available 1,3-dienes to be used as starting materials for the synthesis of 1,4-benzodiazepin-5-ones, only the second such method to be published,[21] and the first that utilises easily accessible *N*-sulfinyl dienophiles.

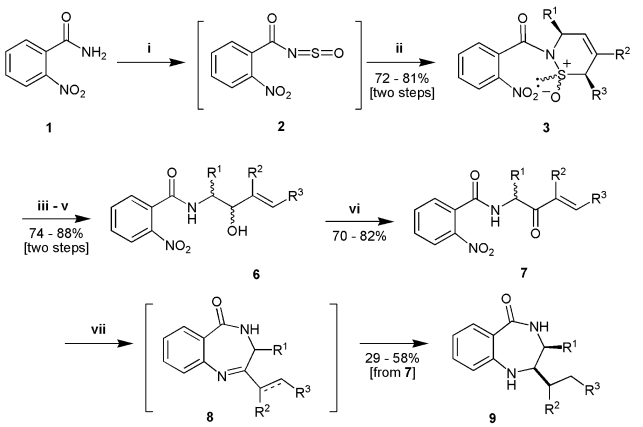
2. Results and discussion

We envisaged (see Scheme 1) that the 2-(*o*-nitroaroyl)-1,2-thiazine-1-oxides **3** would be excellent precursors for the synthesis of the (*o*-nitrobenzamido)carbonyl cyclisation precursors **7** via the intermediate (*o*-nitrobenzamido)-alcohols **6**. The alcohols **6** would be formed from the 1,2-thiazine-1-oxides **3** via ring opening with a Grignard reagent, [2,3]-sigmatropic rearrangement of the resultant sulfoxide **4**, and desulfurisation[34] of the rearranged product, the sulfenate ester **5**. The requisite 2-(*o*-nitroaroyl)-1,2-thiazine-1-oxides **3** would be made available via the hetero-Diels–Alder reaction of the *N*-sulfinyl dienophile **2** with a variety of dienes, where the *N*-sulfinyl compound should easily be formed from the reaction of *o*-nitrobenzamide **1** with thionyl chloride.[35]



Scheme 1. Proposed route to (*o*-nitrobenzamido)ketones **7**.

Thus, as shown in Scheme 2, *o*-nitrobenzamide **1** was reacted under anhydrous conditions with thionyl chloride and pyridine in THF at room temperature for 4 h to give *N*-sulfinyl compound **2**. Compound **2** could not be purified



Scheme 2. Synthesis of 1,4-benzodiazepin-5-ones **9** from 1,2-thiazine-1-oxides **3**. Reagents and Conditions: (i) $SOCl_2$, pyridine, THF, room temperature, 4 h. (ii) $R^1HC{=}{=}CH{-}CR^2{=}CHR^3$, THF, room temperature, overnight. (iii) PhMgBr, THF, −40 °C, 3 h. (iv) Sat. NH_4Cl(aq.). (v) MeOH, $P(OMe)_3$, 60 °C, 10–15 h. (vi) Dess–Martin periodinane, CH_2Cl_2, room temperature, 1 h. (vii) H_2, Pd/C, MeOH, room temperature, 16–20 h.

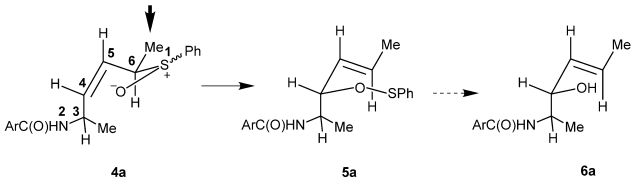
and was extremely unstable, undergoing facile hydrolysis (over 10 to 15 min) in the air to liberate sulfur dioxide and *o*-nitrobenzamide, the products of hydrolysis. However, rapid analysis of the reaction mixture by infrared spectroscopy showed the total disappearance of the sulfonamide $-NH_2$ group after 4–5 h and the appearance of a band (1176 cm^{-1}) characteristic[35] of the –N═S═O group. At this point, the appropriate diene [(*E*,*E*)-2,4-hexadiene, (*E*)-1,3-pentadiene, isoprene or butadiene] was added into the mixture. Hetero-Diels–Alder reaction proceeded smoothly under anhydrous conditions, after which chromatographic work-up yielded the required 2-(*o*-nitroaroyl)-1,2-thiazine-1-oxides **3** in good to excellent yields for the purified compounds over the two steps (4 examples, see Table 1). Due to the fact that our target ketones **7** have only one chiral centre, we did not need to confirm the stereochemical outcome of the cycloaddition reaction. However, those cycloadducts **3** with more than one chiral centre, i.e. compounds **3a** and **3b** (see Table 1), were formed as single diastereoisomers, an observation in keeping with other *N*-sulfinyl cycloadditions.[34,35]

Next, also shown in Scheme 2, the purified 2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxides **3** were treated with phenylmagnesium bromide in THF at low temperature (−40 °C). Aqueous work-up and treatment of the dried crude product with hot methanolic trimethyl phosphite[34] gave the (*o*-nitrobenzamido)alcohols **6**. The products **6** were consistent with the thiazine **3** having undergone ring opening to give the allylic sulfoxide **4**, shown previously in Scheme 1, followed by a thermally allowed (reversible) [2,3]-sigmatropic rearrangement to give intermediate sulfenate ester **5**, also shown in Scheme 1. Trimethyl phosphite mediated

Table 1. % Yields for pure and isolated compounds **3**, **6**, **7** and **9**

Entry	R^1	R^2	R^3	% Yield of thiazine **3** (from **1**)	% Yield of alcohol **6** (from **3**)	% Yield of ketone **7** (from **6**)	% Yield of benzodiazepine **9** (from **7**)
a	Me	H	Me	77	88	82	47
b	Me	H	H	81	74	75	58
c	H	Me	H	75	85	72	29
d	H	H	H	72	76	70	40

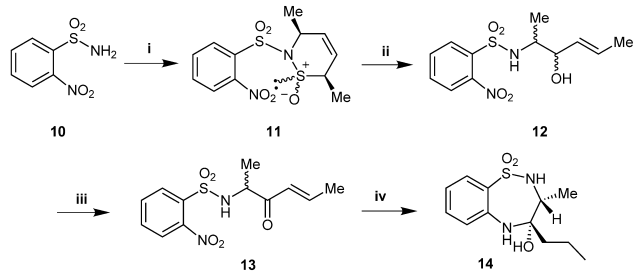
(irreversible) desulfurisation of the intermediate sulfenate esters **5** gave the (*o*-nitrobenzamido)alcohols **6**. We made no attempt to purify or characterise the intermediates **4** or **5** since the overall yields obtained for the purified (*o*-nitrobenzamido)alcohols **6** were consistently excellent for this three-step process (see Table 1). The relative stereochemistry of compounds **6a** and **6b** (R^1=Me) was not determined as, at the next stage, the alcohol chiral center was to be oxidised. It is of interest to note, however, that others have reported that this sequence of reactions proceeds with a high degree of stereoselectivity when performed with other substrates,[34–36] a point reflected by the fact that we found compounds **6a** and **6b** to be single diasteroisomers. In the one case where it is appropriate, i.e. for compound **6a** (R^2=H, R^3=Me), the alkene geometry of compound **6** was found to be (*E*). This can be explained[34] by invoking a 5-membered ring envelope transition state for the [2,3]-sigmatropic rearrangement, in which the methyl group that occupies position 6 (see Scheme 3) is in a pseudo-equatorial position leading to (*E*)-alkene geometry in the sulfenate ester **5a** and, subsequently, in the alcohol **6a**.



Scheme 3. The formation of (*E*)-alkene **6a**.

Oxidation of the purified alcohols **6**, as per Scheme 2, was best achieved with Dess–Martin periodinane, giving the corresponding (*o*-nitrobenzamido)ketones **7** in good yields (Table 1). Exposure of the (*o*-nitrobenzamido)ketones **7** to hydrogenation at atmospheric pressure using 5% palladium over activated carbon resulted in reduction of the nitro group to the amine, ring closure to a cyclic imine followed by reduction of imine bond, and accompanying reduction of the exocyclic olefinic double bond. These four steps gave, as the only isolated products, the 1,2,3,4-tetrahydro-1,4-benzodiazepin-5-ones **9**, as shown in Scheme 2. Where relevant (i.e. for compounds **9a** and **9b**, R^1=Me, R^2=H, R^3=Me/H), a single diastereoisomer was isolated, and the relative stereochemistry of the groups at positions 2 and 3 of the 1,4-benzodiazepin-5-one was assigned *cis*/*syn* on the basis of nOe experiments. Thus, clear signal enhancements were observed between the C3 R^1 methyl protons and the C2-bound CH_2 group (R^2=H), but not between the C3 R^1 methyl and the C2 proton, nor between the C3 proton and the C2-bound CH_2 group. The observed stereochemistry is in line with the expected delivery of hydrogen to the face of the imine bond in intermediate **8** that is opposite to the existing methyl group at C3. The yields (Table 1) were fair considering the four-step nature of the reaction and, furthermore, considering that similar (*o*-nitrobenzamido)-carbonyl reductive cyclisations reported in the literature often give bicyclic 1,4-benzodiazepin-5-one yields in approximately the same range.[4,14,17]

In an attempt to extend the scope of this methodology, we also synthesised the 2-(*o*-nitrobenzenesulfonyl)-1,2-thiazine-1-oxide **11** (60% yield from **10**; single diastereoisomer), as shown in Scheme 4, and subjected it to the same sequence of reactions as was applied to the 2-(*o*-nitroaroyl)-1,2-thiazine-1-oxides **3**. This gave access to the 2-(*o*-nitrobenzenesulfonamido)alcohol **12** in 89% yield from the thiazine **11**. Dess–Martin periodinane oxidation proceeded in 84% yield to give the 2-(*o*-nitrobenzenesulfonamido)ketone **13**. Compound **13** was treated with hydrogen and palladium over activated carbon. Intriguingly, and anomalous to the corresponding (*o*-nitrobenzamido) systems **7a–d**, this gave the carbinolamine 1,2,3,4-tetrahydro-4-hydroxy-1,2,5-benzothiadiazepin-1,1-dioxide **14** in 45% yield. The product was isolated as a single diastereoisomer. The stereochemistry was assigned on the basis of nOe experiments that showed a clear enhancement between the CH proton at position 3 of the 1,2,5-benzothiadiazepine ring and the C4-bound CH_2 group of the C4 *n*-propyl substituent, but not between the methyl group at position 3 and the same CH_2 group.



Scheme 4. Synthesis of 4-hydroxy-1,2,5-benzothiadiazepin-1,1-dioxide **14**. Reagents and conditions: (i) (a) $SOCl_2$, benzene, reflux, 72 h; (b) (*E*,*E*)-2,4-hexadiene, room temperature, 14 h. (ii) (a) PhMgBr, THF, −40 °C, 2 h; (b) Sat. NH_4Cl(aq.); (c) $P(OMe)_3$, MeOH, 60 °C, 5 h. (iii) Dess–Martin periodinane, CH_2Cl_2, room temperature, 30 min. (iv) H_2, Pd/C, MeOH, room temperature, 4 h.

3. Conclusion

In summary, we have shown that 2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxides, which are readily available from *o*-nitrobenzamide and diene feedstocks, are easily transformed into *o*-nitrobenzamido alkenones that are readily ring closed to give 1,2,3,4-tetrahydro-1,4-benzodiazepin-5-ones in moderate to good yield. This constitutes a new route to this important sub-set of the 'privileged' 1,4-benzodiazepine pharmacophore and adds to the diversity of structures available. The method is also applicable to the synthesis of 1,2,5-benzothiadiazepines, although in this case, ring closure gives the 4-hydroxy compound. We are currently exploring this latter process further, together with other 1,2-thiazine-1-oxide based routes to 1,2,5-benzothiadiazepin-1,1-dioxides and will report our results in due course.

4. Experimental

4.1. General instructions

^{1}H NMR spectra were recorded on a Bruker AC-250 (250 MHz) or a Bruker Advance DPX-400 (400 MHz) spectrometer using deuterochloroform as solvent with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on a Bruker AC-250 (63 MHz) or a Bruker

Advance DPX-400 (100 MHz) spectrometer using deuterochloroform as solvent, referencing to the deuterochloroform lock. Coupling constants (*J*) are reported in Hertz (Hz). Low resolution mass spectra were performed on a Micromass Quattro II triple quadrupole mass spectrometer, and high resolution mass spectra were recorded on a Finnegan MAT 900 XLT instrument operated at the EPSRC National Mass Spectrometry Service Center, Swansea. Flash silica chromatography was performed using Merck Kieselgel 60. Thin layer chromatography was carried out with Camlab 0.25 mm silica gel (F_{254}) coated plastic or aluminium plates, using petroleum ether (40–60°)/ethyl acetate as eluent, and were visualised using ultraviolet light or a vanillin stain. All reagents and reaction solvents were purchased from Sigma-Aldrich and solvents for chromatography were purchased from Merck. Petroleum ether and ethyl acetate were purchased as AR grade and were used as received. Reactions were routinely carried out under an atmosphere of dry, oxygen-free, nitrogen, unless otherwise stated. All new compounds were isolated by flash silica chromatography as one spot pure compounds (TLC) and were single pure compounds (>98% purity) by ^{1}H NMR and ^{13}C NMR spectroscopy.

4.2. Synthesis of 2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxides 3

A solution of *o*-nitrobenzamide (~9–9.3 mmol, 1.0 equiv.) and anhydrous pyridine (6.0 equiv.) in anhydrous tetrahydrofuran (15 ml), under an atmosphere of dry nitrogen, was prepared. To this solution was added, dropwise with stirring over a period of 3–4 h, a solution of freshly distilled thionyl chloride (1.5 equiv.) in anhydrous tetrahydrofuran (5 ml), to yield the crude *N*-sulfinyl compound. The crude reaction mixture was stirred for 30 min, followed by dropwise addition of the appropriate 1,3-diene (1.6 equiv., except for butadiene where 10 equiv. were condensed into the reaction flask), and the whole was stirred at room temperature for 16 h, whilst being monitored by TLC. After completion of the reaction, the solvent was removed in vacuo and the crude product was purified by flash silica chromatography (eluent PE/EtOAc 1:1). The following products were obtained:

4.2.1. 3,6-Dihydro-3,6-dimethyl-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide 3a. Obtained, after column chromatographic purification (single spot by TLC), as a white solid (2.0335 g, 77%) from *o*-nitrobenzamide (1.5000 g, 9.03 mmol, 1.0 equiv.) and 2,4-hexadiene (*d*=0.720, 1.65 ml, 14.45 mmol, 1.6 equiv.). Mp: 154–156 °C.

δ_H (250 MHz, $CDCl_3$): 1.30 (d, 3H, *J*=7.2 Hz, Me), 1.68 (d, 3H, *J*=6.4 Hz, Me), 3.45 (dquint, 1H, *J*=7.2, 1.0 Hz, C*H*Me), 4.72 (dquint, 1H, *J*=5.7, 0.9 Hz, C*H*Me), 5.92 (ddd, 1H, *J*=10.6, 7.2, 0.6 Hz, C=C*H*), 6.25 (dd, 1H, *J*=10.6, 4.8 Hz, C=C*H*), 7.61–7.70, (m, 2H, 2×ArH), 7.79 (dt, 1H, *J*=7.7, 1.2 Hz, 1×ArH), 8.23 (dd, 1H, *J*=7.3, 1.6 Hz, 1×ArH). δ_C (63 MHz, $CDCl_3$): 15.7 (CH_3), 20.7 (CH_3), 48.9 (CH), 54.4 (CH), 119.6 (CH), 124.6 (CH), 128.1 (quat.), 129.5 (CH), 130.7 (CH), 131.5 (quat.), 132.4 (CH), 134.7 (CH), 145.5 (quat.), 170.4 (quat.). υ_{max} (KBr disc, cm^{-1}): 3019, 1677, 1532, 1350, 1216, 1092, 669. EI mass spectrum (*m*/*z*, %): 295 ($M+H^+$, 1%), 269 (5%), 104 (45%), 150 (95%), 82 (100%), 76 (85%). HRMS (ES+): found MH^+ 295.0755, $C_{13}H_{14}N_2SO_4$ requires MH^+ 295.0753.

4.2.2. 3,6-Dihydro-3-methyl-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide 3b. Obtained, after column chromatographic purification (single spot by TLC), as a pale yellow solid (2.0961 g, 81%) from *o*-nitrobenzamide (1.5163 g, 9.13 mmol, 1.0 equiv.) and 1,3-pentadiene (*d*=0.683, 1.46 ml, 14.60 mmol, 1.6 equiv.). Mp: 130–132 °C.

δ_H (250 MHz, $CDCl_3$): 1.55 (d, 3H, *J*=6.5 Hz, Me), 3.49 (dt, 1H, *J*=3.0, 1.2 Hz, C*H*H), 3.55 (dd, 1H, *J*=7.4, 1.2 Hz, C*H*H), 4.97 (dquint, 1H, *J*=6.4, 0.9 Hz, C*H*Me), 5.93 (ddd, 1H, *J*=10.0, 7.4, 3.2 Hz, C=C*H*), 6.55 (ddd, 1H, *J*=10.0, 6.2, 2.8 Hz, C=C*H*), 7.58–7.70 (m, 2H, 2×ArH), 7.78 (dt, 1H, *J*=7.5, 1.2 Hz, 1×ArH), 8.25 (dd, 1H, *J*=8.3, 1.1 Hz, 1×ArH). δ_C (63 MHz, $CDCl_3$): 18.2 (CH_3), 47.8 (CH_2), 49.6 (CH), 115.0 (CH), 124.6 (CH), 129.5 (CH), 130.8 (CH), 131.5 (quat.), 134.7 (CH), 134.9 (CH), 145.1 (quat.), 168.7 (quat.). υ_{max} (KBr disc, cm^{-1}): 3017, 1654, 1533, 1349, 1317, 1216, 1147, 1099, 859, 668. EI mass spectrum (*m*/*z*, %): 281 ($M+H^+$, 1%), 233 (3%), 215 (20%), 150 (50%), 104 (35%), 82 (30%), 76 (100%). HRMS (ES+): found MH^+ 281.0597, $C_{12}H_{12}N_2SO_4$ requires MH^+ 281.0596.

4.2.3. 3,6-Dihydro-5-methyl-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide 3c. Obtained, after column chromatographic purification (single spot by TLC), as a beige solid (1.9410 g, 75%) from *o*-nitrobenzamide (1.5419 g, 9.28 mmol, 1.0 equiv.) and isoprene (*d*=0.681, 1.49 ml, 14.85 mmol, 1.6 equiv.). Mp: 128–130 °C.

δ_H (250 MHz, $CDCl_3$): 1.94 (s, 3H, Me), 3.23 (d, 1H, *J*=15.1 Hz, C*H*H), 3.41 (bd, 1H, *J*=15.4 Hz, C*H*H), 4.14 (dt, 1H, *J*=17.6, 1.2 Hz, C*H*H), 4.68 (bd, 1H, *J*=17.8 Hz, C*H*H), 5.86 (s, 1H, C=C*H*), 7.51 (d, 1H, *J*=7.5 Hz, 1×ArH), 7.67 (dt, 1H, *J*=8.2, 1.4 Hz, 1×ArH), 7.77 (dt, 1H, *J*=7.5, 1.1 Hz, 1×ArH), 8.15 (dd, 1H, *J*=8.3, 1.1 Hz, 1×ArH). δ_C (63 MHz, $CDCl_3$): 25.0 (CH_3), 38.6 (CH_2), 53.5 (CH_2), 119.0 (CH), 123.0 (quat.), 125.1 (CH), 128.9 (CH), 131.1 (CH), 131.9 (quat.), 135.2 (CH), 145.6 (quat.), 167.5 (quat.). υ_{max} (KBr disc, cm^{-1}): 3018, 1664, 1531, 1347, 1326, 1216, 1105, 1090, 850, 668. EI mass spectrum (*m*/*z*, %): 281 ($M+H^+$, 1%), 233 (2%), 150 (20%), 104 (20%), 82 (30%), 76 (100%). HRMS (ES+): found MH^+ 281.0591, $C_{12}H_{12}N_2SO_4$ requires MH^+ 281.0596.

4.2.4. 3,6-Dihydro-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide 3d. Obtained, after column chromatographic purification (single spot by TLC), as pale yellow prisms (1.7418 g, 72%) from *o*-nitrobenzamide (1.5022 g, 9.04 mmol, 1.0 equiv.) and 1,3-butadiene (4.89 g, 10 equiv.). Mp: 136–138 °C.

δ_H (250 MHz, $CDCl_3$): 3.46–3.52 (m, 2H, 2×C*H*H), 4.15 (dhextet, 1H, *J*=18.5, 1.8 Hz, C*H*H), 4.84 (bd, 1H, *J*=18.1 Hz, C*H*H), 5.79–5.89 (m, 1H, C=C*H*), 6.23 (dd, 1H, *J*=8.1, 1.7 Hz, C=C*H*), 7.40 (d, 1H, *J*=7.5 Hz, 1×ArH), 7.67 (ddd, 1H, *J*=8.2, 7.6, 1.5 Hz, 1×ArH), 7.80 (dt, 1H, *J*=7.5, 1.2 Hz, 1×ArH), 8.24 (dd, 1H, *J*=8.2, 1.2 Hz, 1×ArH). δ_C (63 MHz, $CDCl_3$): 37.8 (CH_2), 49.3 (CH_2), 114.3 (CH), 124.8 (CH), 125.4 (CH), 128.5 (CH), 130.9 (CH), 131.4 (quat.), 134.8 (CH), 144.9 (quat.), 167.0 (quat.).

υ_{max} (KBr disc, cm^{-1}): 3019, 1682, 1531, 1348, 1311, 1152, 1100, 1095, 669. EI mass spectrum (*m*/*z*, %): 267 ($M+H^+$, 2%), 219 (25%), 150 (100%), 104 (35%), 82 (30%), 76 (40%). HRMS (ES+): found MH^+ 267.0441, $C_{11}H_{10}N_2SO_4$ requires MH^+ 267.0439.

4.2.5. 3,6-Dihydro-3,6-dimethyl-2-(*o*-nitrobenzenesulfonyl)-1,2-thiazine-1-oxide 11. *o*-Nitrobenzenesulfonamide (1.0000 g, 4.95 mmol, 1.0 eq) and thionyl chloride (1.5 equiv.) were heated in anhydrous benzene (15 ml) at reflux for 72 h. The mixture was cooled to room temperature and the solvent and excess thionyl chloride were removed in vacuo. The residue was dissolved in freshly distilled anhydrous THF (10 ml). 2,4-Hexadiene (*d*=0.720, 0.90 ml, 7.91 mmol, 1.6 equiv.) was added, and the mixture was stirred at room temperature for 14 h. The crude product was purified by flash silica chromatography (eluent PE/EtOAc 6:5) to give the pure product as a pale yellow solid (0.9830 g, 60%). Mp: 110–112 °C.

δ_H (400 MHz, $CDCl_3$): 1.39 (d, 3H, *J*=7.4 Hz, Me), 1.56 (d, 3H, *J*=7.0 Hz, Me), 3.29–3.41 (m, 1H, C*H*Me), 4.57 (dquint, 1H, *J*=6.8, 3.4 Hz, C*H*Me), 5.45 (ddd, 1H, *J*=11.0, 2.5, 2.0 Hz, C=C*H*), 5.96 (ddd, 1H, *J*=11.0, 3.4, 2.9 Hz, C=C*H*), 7.71–7.91 (m, 3H, 3×ArH), 8.19 (dd, 1H, *J*=8.3, 1.1 Hz, 1×ArH). δ_C (100 MHz, $CDCl_3$): 15.7 (CH_3), 23.5 (CH_3), 51.8 (CH), 53.1 (CH), 119.5 (CH), 124.8 (CH), 129.5 (CH), 131.3 (CH), 132.5 (CH), 133.0 (quat), 134.8 (CH), 147.6 (quat.). υ_{max} (KBr disc, cm^{-1}): 3019, 1531, 1332, 1311, 1156, 1106, 1095, 753, 669. EI mass spectrum (*m*/*z*, %): 331 ($M+H^+$, 2%), 282 (2%), 229 (35%), 186 (20%), 82 (100%), 67 (85%). HRMS (CI+[NH_3]): found MH^+ 331.0419, $C_{12}H_{14}N_2O_5S_2$ requires MH^+ 331.0422.

4.3. Synthesis of (*o*-nitrobenzamido)alkenols 6

A solution of phenylmagnesium bromide (3 M solution in ether, 2.0 equiv.) was added with stirring to a solution of the 2-(*o*-nitrobenzoyl)-3,6-dihydro-1,2-thiazine-1-oxide (1.5–3.5 mmol, 1.0 equiv.) in anhydrous tetrahydrofuran (10 ml) at −78 °C under an atmosphere of dry nitrogen. The reaction mixture was kept at low temperature (~−40 °C) for 3 h, whilst being monitored by TLC. Upon completion of the reaction, the mixture was quenched at −20 °C with saturated ammonium chloride solution (15 ml) and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (2×10 ml) and washed with water (2×10 ml) and brine (10 ml). The organic phase was collected, dried ($MgSO_4$), filtered and the solvent evaporated off to yield the allylic sulfoxide, which was not purified further. To a solution of this crude allylic sulfoxide in anhydrous methanol (10 ml) was added trimethyl phosphite (*d*=1.052, 2.0 equiv.), under an atmosphere of dry nitrogen, and the whole was heated under reflux for a total of 10–15 h, and was monitored by TLC. Upon completion of the reaction, the solvent was removed in vacuo and the crude product was purified by column chromatography (eluent: PE/EtOAc 3:2) to yield the (*o*-nitrobenzamido)alkenols as follows:

4.3.1. (*E*)-5-(*o*-Nitrobenzamido)-hex-2-en-4-ol 6a. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.7900 g, 88%) from 3,6-dihydro-3,6-dimethyl-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide **3a** (1.0000 g, 3.40 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.30 (d, 3H, *J*=6.6 Hz, Me), 1.74 (dd, 3H, *J*=6.4, 1.1 Hz, Me), 2.27 (bs, 1H, OH), 4.05–4.25 (m, 2H, C*H*Me and C*H*OH), 5.61 (ddd, 1H, *J*=14.6, 6.0, 1.5 Hz, =C*H*CHOH), 5.77 (dq, 1H, *J*=14.8, 6.2 Hz, =C*H*Me), 6.18 (bd, 1H, *J*=8.0 Hz, NH), 7.49 (dd, 1H, *J*=7.3, 1.7 Hz, ArH), 7.56 (dt, 1H, *J*=7.8, 1.6 Hz, ArH), 7.66 (dt, 1H, *J*=7.4, 1.3 Hz, ArH), 8.04 (dd, 1H, *J*=8.1, 1.2 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 17.3 (CH_3), 17.8 (CH_3), 50.2 (CH), 75.2 (CHOH), 124.5 (CH), 128.7 (CH), 129.2 (CH), 130.4 (CH), 130.6 (CH), 133.1 (quat.), 133.6 (CH), 146.5 (quat.), 166.4 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3380 (broad), 3268, 2978, 2932, 1645, 1532, 1450, 1349, 1260, 1146, 1112, 1093, 972, 788, 702. EI mass spectrum (*m*/*z*, %): 265 (MH^+, 1%), 193 (25%), 150 (100%), 121 (25%), 104 (35%), 76 (30%). HRMS (ES+): found MH^+ 265.1188, $C_{13}H_{16}N_2O_4$ requires MH^+ 265.1188.

4.3.2. 4-(*o*-Nitrobenzamido)-pent-1-en-3-ol 6b. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.3300 g, 74%) from 3,6-dihydro-3-methyl-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide **3b** (0.5000 g, 1.78 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.36 (d, 3H, *J*=6.6 Hz, Me), 5.26 (dq, 1H, *J*=9.8, 1.5 Hz, C*H*Me), 5.40 (qt, 1H, *J*=8.6, 1.2 Hz, C*H*OH), 5.89 (dd, 1H, *J*=16.0, 5.2 Hz, *H*HC=CHCHOH), 5.97 (ddd, 1H, *J*=15.9, 5.4, 1.1 Hz, =C*H*CHOH), 6.04 (m, 1H, *H*HC=CHCHOH), 6.15 (bs, 1H, NH), 7.51–7.68 (m, 3H, 3×ArH), 8.07 (dd, 1H, *J*=8.1, 1.2 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 17.1 (CH_3), 54.2 (CH), 76.4 (CH), 122.8 (CH), 124.1 (CH), 126.0 (CH), 128.6 (CH), 129.1 (quat.), 130.2 (CH), 132.3 (CH), 142.6 (quat.), 167.4 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3388 (broad), 3318 (broad), 2925, 2870, 1651, 1537, 1454, 1377, 1349, 1261, 1216, 1041, 699. EI mass spectrum (*m*/*z*, %): 251 (MH^+, 1%), 193 (35%), 150 (100%), 104 (15%), 76 (20%). HRMS (ES+): found MH^+ 251.1032, $C_{12}H_{14}N_2O_4$ requires MH^+ 251.1032.

4.3.3. 2-Methyl-4-(*o*-nitrobenzamido)-but-1-en-3-ol 6c. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.6050 g, 85%) from 3,6-dihydro-5-methyl-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide **3c** (0.8000 g, 2.85 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.79 (s, 3H, Me), 2.18 (bs, 1H, OH), 3.36 (ddd, 1H, *J*=13.8, 7.6, 4.9 Hz, C*H*H), 3.81 (ddd, 1H, *J*=13.8, 6.8, 3.4 Hz, CH*H*), 4.33 (dd, 1H, *J*=7.5, 3.4 Hz, C*H*OH), 4.97 (s, 1H, C=CH_2), 5.10 (s, 1H, C=CH_2), 6.39 (bs, 1H, NH), 7.50–7.64 (m, 2H, 2×ArH), 7.66 (dt, 1H, *J*=7.4, 1.3 Hz, ArH), 8.04 (dd, 1H, *J*=8.0, 1.3 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 18.6 (CH_3), 44.2 (CH_2), 73.8 (CH), 111.9 (CH_2), 124.6 (CH), 128.8 (CH), 130.5 (CH), 132.9 (quat.), 133.7 (CH), 144.8 (quat.), 146.8 (quat.), 167.1 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3396 (broad), 3304 (broad), 3087, 2921, 1654, 1532, 1442, 1350, 1314, 1083, 1055, 907, 858, 789, 699. EI mass spectrum (*m*/*z*, %): 251(MH^+, 1%), 151 (70%), 150 (100%), 121 (45%), 104 (40%), 76 (72%). HRMS (CI+[NH_3]): found MH^+ 251.1036, $C_{12}H_{14}N_2O_4$ requires MH^+ 251.1032.

4.3.4. 4-(*o*-Nitrobenzamido)-but-1-en-3-ol 6d. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.3370 g, 76%) from 3,6-dihydro-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide **3d** (0.5000 g, 1.88 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 2.55 (bs, 1H, OH), 3.31 (ddd, 1H, *J*=13.8, 7.7, 5.1 Hz, C*H*H), 3.78 (ddd, 1H, *J*=13.8, 7.6, 3.5 Hz, CH*H*), 4.39–4.46 (m, 1H, C*H*OH), 5.24 (dt, 1H, *J*=10.5, 1.4 Hz, C=CH_2), 5.38 (dt, 1H, *J*=17.2, 1.4 Hz, C=CH_2), 5.89 (ddd, 1H, *J*=17.2, 10.5, 5.5 Hz, H_2C=C*H*CHOH), 6.58 (bs, 1H, NH), 7.54 (dt, 1H, *J*=7.3, 1.5 Hz, ArH), 7.59–7.70 (m, 2H, 2×ArH), 8.05 (dd, 1H, *J*=8.0, 1.3 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 45.5 (CH_2), 71.4 (CH), 116.6 (CH), 124.6 (CH), 128.8 (CH), 130.5 (CH), 133.7 (quat.), 133.8 (CH), 137.6 (CH), 146.5 (quat.), 167.2 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3360 (broad), 3309 (broad), 3086, 3013, 2929, 1651, 1530, 1349, 1313, 1048, 930, 857, 788, 698. EI mass spectrum (*m*/*z*, %): 237 (MH^+, 2%), 151 (25%), 152 (65%), 121 (20%), 104 (50%), 76 (100%), 57 (54%). HRMS (ES+): found MH^+ 237.0875, $C_{11}H_{12}N_2O_4$ requires MH^+ 237.0875.

4.3.5. (*E*)-5-(*o*-Nitrobenzenesulfamido)-hex-2-en-4-ol 12. This was obtained by the identical procedure except that, at the trimethyl phosphite stage, the reaction was noted to be complete after 5 h. Chromatographic purification gave the product (single spot by TLC) as a yellow oil (0.8100 g, 89%) from 3,6-dihydro-3,6-dimethyl-2-(*o*-nitrobenzenesulfonyl)-1,2-thiazine-1-oxide **11** (1.0000 g, 3.03 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.15 (d, 3H, *J*=6.7 Hz, Me), 1.58 (dd, 3H, *J*=6.4, 1.5 Hz, Me), 1.82 (bs, 1H, OH), 3.49 (dquint, 1H, *J*=6.7, 5.0 Hz, C*H*Me), 3.95 (dd, 1H, *J*=7.3, 5.0 Hz, C*H*OH), 5.35 (ddq, 1H, *J*=15.2, 7.4, 1.6 Hz, *H*C=CHMe), 5.61 (bd, 1H, *J*=7.9 Hz, NH), 5.70 (qdd, 1H, *J*=15.2, 6.5, 0.8 Hz, HC=C*H*Me), 7.72–7.78 (m, 2H, 2×ArH), 7.85–7.90 (m, 1H, ArH), 8.13–8.17 (m, 1H, ArH). δ_C (100 MHz, $CDCl_3$): 17.8 (CH_3), 18.2 (CH_3), 55.1 (CH), 75.5 (CH), 125.3 (CH), 129.6 (CH), 130.4 (CH), 130.7 (CH), 132.8 (CH), 133.3 (CH), 134.7 (quat.), 149.0 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3389 (broad), 3327 (broad), 3045, 2996, 1547, 1449, 1346, 1287, 1180, 1108, 1027, 780, 662. EI mass spectrum (*m*/*z*, %): 301 (MH^+, 3%), 229 (33%), 218 (20%), 186 (100%), 109 (55%), 84 (41%), 76 (20%). HRMS (CI+[NH_3]): found MNH_4^+ 318.1129, $C_{12}H_{14}N_2O_5S$ requires MNH_4^+ 318.1125.

4.4. Synthesis of (*o*-nitrobenzamido)alkenones 7

To a solution of Dess–Martin periodinane (1.1 equiv.) in dry dichloromethane (10 ml) was added a solution of the allylic alcohol (1–2 mmol, 1 equiv.) in dry dichloromethane (5 ml) at room temperature. The reaction mixture was stirred at room temperature for 0.5–1 h, whilst being monitored by TLC. The solvent was evaporated off and the crude product was purified by column chromatography (eluent: PE/EtOAc 3:2) to yield the following products:

4.4.1. (*E*)-5-(*o*-Nitrobenzamido)-hex-2-en-4-one 7a. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.4070 g, 82%) from (*E*)-5-(*o*-nitrobenzamido)-hex-2-en-4-ol **6a** (0.5000 g, 1.89 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.54 (d, 3H, *J*=7.1 Hz, Me), 1.99 (dd, 3H, *J*=6.9, 1.5 Hz, Me), 5.05 (quint., 1H, *J*=7.0 Hz, C*H*Me), 6.26 (dq, 1H, *J*=15.7, 1.6 Hz, MeHC=C*H*CO), 6.88 (bs, 1H, NH), 7.11 (dq, 1H, *J*=15.5, 6.9 Hz, Me*H*C=CH), 7.52–7.72 (m, 3H, 3×ArH), 8.10 (d, 1H, *J*=8.0 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 18.2 (CH_3), 18.6 (CH_3), 52.8 (CH), 124.6 (CH), 127.8 (CH), 128.7 (CH), 130.6 (CH), 132.7 (quat.), 133.7 (CH), 146.3 (quat.), 146.6 (CH), 165.7 (quat.), 197.0 (quat). υ_{max} (NaCl plates, neat, cm^{-1}): 3321 (broad), 3018, 2928, 1654, 1532, 1444, 1349, 1217, 1078, 970, 667. EI mass spectrum (*m*/*z*, %): 263 (MH^+, 2%), 193 (25%), 150 (100%), 104 (15%), 76 (15%), 69 (35%). HRMS (ES+): found MH^+ 263.1030, $C_{13}H_{14}N_2O_4$ requires MH^+ 263.1032.

4.4.2. 4-(*o*-Nitrobenzamido)-pent-1-en-3-one 7b. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.2225 g, 75%) from 4-(*o*-nitrobenzamido)-pent-1-en-3-ol **6b** (0.3000 g, 1.20 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.56 (d, 3H, *J*=7.1 Hz, Me), 5.14 (quint., 1H, *J*=7.1 Hz, CH*Me*), 6.02 (dd, 1H, *J*=8.1, 3.5 Hz, C=C*H*), 6.49–6.52 (m, 2H, 2×C=C*H*), 6.84 (bs, 1H, NH), 7.52–7.73 (m, 3H, 3×ArH), 8.09 (dd, 1H, *J*=8.0, 1.3 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 18.0 (CH_3), 52.1 (CH), 124.7 (CH), 128.7 (CH), 130.6 (CH), 131.3 (CH), 132.5 (CH), 133.8 (CH), 134.0 (quat.), 143.3 (quat.), 168.2 (quat.), 197.6 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3324 (broad), 2924, 1650, 1531, 1349, 1075, 852, 789, 699. EI mass spectrum (*m*/*z*, %): 249 (MH^+, 2%), 193 (35%), 150 (100%), 76 (65%), 55 (90%). HRMS (CI+[NH_3]): found MNH_4^+ 266.1140, $C_{12}H_{12}N_2O_4$ requires MNH_4^+ 266.1141.

4.4.3. 2-Methyl-4-(*o*-nitrobenzamido)-but-1-en-3-one 7c. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.2500 g, 72%) from 2-methyl-4-(*o*-nitrobenzamido)-but-1-en-3-ol **6c** (0.3500 g, 1.40 mmol, 1.0 equiv.).

δ_H (270 MHz, $CDCl_3$): 1.93 (s, 3H, Me), 4.69 (d, 1H, *J*=4.4 Hz, CH_2), 5.94 (d, 1H, *J*=1.5 Hz, C=C*H*H), 6.12 (s, 1H, C=CH*H*), 6.91 (bs, 1H, NH), 7.56–7.61 (m, 2H, 2×ArH), 7.68 (dt, 1H, *J*=7.5, 1.2 Hz, ArH), 8.05 (dd, 1H, *J*=8.0, 0.8 Hz, ArH). δ_C (63 MHz, $CDCl_3$): 17.2 (CH_3), 46.0 (CH_2), 124.5 (CH), 126.5 (CH_2), 128.7 (CH), 130.6 (CH), 132.4 (quat.), 133.6 (CH), 142.0 (quat.), 146.5 (quat.), 166.3 (quat.), 195.0 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3306 (broad), 2927, 1657, 1532, 1349, 1075, 1052, 857, 789, 699. EI mass spectrum (*m*/*z*, %): 249 (MH^+, 2%), 193 (35%), 150 (100%), 120 (20%), 104 (25%), 76 (65%). HRMS (CI+[NH_3]): found MNH_4^+ 266.1140, $C_{12}H_{12}N_2O_4$ requires MNH_4^+ 266.1141.

4.4.4. 4-(*o*-Nitrobenzamido)-but-1-en-3-one 7d. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.1736 g, 70%) from 4-(*o*-nitrobenzamido)-but-1-en-3-ol **6d** (0.2500 g, 1.06 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 4.62 (d, 2H, *J*=4.4 Hz, CH_2), 6.07 (t,

1H, *J*=3.8 Hz, C=C*H*), 6.46 (d, 2H, *J*=3.8 Hz, 2× C=C*H*), 6.79 (bs, 1H, NH), 7.56–7.65 (m, 2H, 2×ArH), 7.71 (dt, 1H, *J*=7.4, 1.3 Hz, ArH), 8.11 (dd, 1H, *J*=8.1, 1.2 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 47.6 (CH_2), 124.7 (CH_2), 127.1 (quat.), 128.7 (CH), 130.8 (CH), 133.6 (CH), 133.8 (CH), 134.8 (CH), 148.8 (quat.), 166.2 (quat.), 193.8 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3301 (broad), 2925, 1654, 1530, 1349, 1260, 856, 790, 699. EI mass spectrum (*m*/*z*, %): 235 (MH^+, 3%), 177 (45%), 166 (25%), 150 (30%), 121 (35%), 105 (70%), 91 (97%), 77 (100%). HRMS (CI+[NH_3]): found MNH_4^+ 252.0990, $C_{11}H_{10}N_2O_4$ requires MNH_4^+ 252.0984.

4.4.5. (E)-5-(*o*-Nitrobenzenesulfamido)-hex-2-en-4-one 13. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.4170 g, 84%) from (*E*)-5-(*o*-nitrobenzenesulfamido)-hex-2-en-4-ol **12** (0.5000 g, 1.67 mmol, 1.0 equiv.).

δ_H (270 MHz, $CDCl_3$): 1.42 (d, 3H, *J*=7.2 Hz, Me), 1.91 (dd, 3H, *J*=6.9, 1.7 Hz, Me), 4.42 (quint., 1H, *J*=7.2 Hz, C*H*Me), 6.15 (dq, 1H, *J*=15.6, 1.6 Hz, *H*C=CHMe), 6.47 (bd, *J*=7.2 Hz, NH), 6.94 (dq, 1H, *J*=15.6, 6.9 Hz, C=C*H*Me), 7.67–7.75 (m, 2H, 2×ArH), 7.87–7.90 (m, 1H, ArH), 8.03–8.07 (m, 1H, ArH). δ_C (63 MHz, $CDCl_3$): 18.6 (CH_3), 19.6 (CH_3), 56.6 (CH), 125.6 (CH), 127.0 (CH), 129.5 (quat.), 130.3 (CH), 132.8 (CH), 133.6 (CH), 134.4 (quat.), 146.3 (CH), 195.8 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3319 (broad), 3021, 2989, 1660, 1552, 1447, 1348, 1318, 1287, 1216, 1180, 1108, 1077, 796, 700, 669. EI mass spectrum (*m*/*z*, %): 299 (MH^+, 1%), 229 (47%), 186 (95%), 109 (20%), 76 (15%), 69 (100%). HRMS (CI+[NH_3]): found MNH_4^+ 316.0965, $C_{12}H_{14}N_2O_5S$ requires MNH_4^+ 316.0967.

4.5. Synthesis of 1,4-benzodiazepin-5-ones 9

A solution of the allylic ketone (0.3–0.8 mmol) in dry methanol (10 ml) at room temperature was treated with 5% palladium on charcoal (~0.1 g) and a slow stream of hydrogen was allowed to pass from a balloon into the reaction mixture. The reaction was monitored by TLC and was showed to be complete after 16–20 hrs, except for compound **14**, the formation of which was complete after 4 h. The reaction mixture was filtered (celite) to remove the catalyst, the solvent was evaporated off and the residue was purified by column chromatography (PE:EtOAc, 1:2). Thus obtained were the following 1,4-benzodiazepin-5-ones:

4.5.1. 1,2,3,4-Tetrahydro-3-methyl-2-(*n*-propyl)-1,4-benzodiazepin-5-one 9a. Obtained, after column chromatographic purification (single spot by TLC), as a white crystalline solid (0.0782 g, 47%) from (*E*)-5-(*o*-nitrobenzamido)-hex-2-en-4-one **7a** (0.2000 g, 0.7626 mmol). Mp: 193–195 °C.

δ_H (400 MHz, $CDCl_3$): 0.97 (t, 3H, *J*=6.9 Hz, Me), 1.22 (d, 3H, *J*=6.9 Hz, Me), 1.25–1.63 (m, 4H, C*H*$_2$C*H*$_2$), 3.39 (dd, 1H, *J*=8.8, 2.5 Hz, C*H*N), 3.70 (quint., 1H, *J*=7.1 Hz, CMe*H*N), 6.29 (bd, 1H, *J*=8.5 Hz, NH), 6.58 (dd, 1H, *J*=8.2, 1.0 Hz, ArH), 6.76 (dt, 1H, *J*=7.3, 1.0 Hz, ArH), 7.23, (dt, 1H, *J*=7.6, 1.6 Hz, ArH), 8.03 (dd, 1H, *J*=8.1, 1.6 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 14.0 (CH_3), 16.8 (CH_3), 19.6 (CH_2), 33.2 (CH_2), 50.6 (CH), 60.6 (CH), 117.5 (CH), 118.0 (CH), 126.1 (quat.), 132.7 (CH), 133.3 (CH), 145.5 (quat.), 169.8 (quat.) υ_{max} (KBr disc, cm^{-1}): 3283, 3126, 2970, 2927, 1628, 1527, 1441, 1260, 1089, 1023, 803. EI mass spectrum (*m*/*z*, %): 219 (MH^+, 10%), 218 (50%), 203 (10%), 175 (30%), 147 (25%), 133 (60%), 132 (65%), 119 (100%), 105 (35%), 91 (55%), 77 (30%), 65 (25%), 57 (35%), 45 (50%). HRMS (ES+): found MH^+ 219.1498, $C_{13}H_{18}N_2O$ requires MH^+ 219.1497.

4.5.2. 2-Ethyl-1,2,3,4-tetrahydro-3-methyl-1,4-benzodiazepin-5-one 9b. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.0716 g, 58%) from 4-(*o*-nitrobenzamido)-pent-1-en-3-one **7b** (0.1500 g, 0.6043 mmol).

δ_H (400 MHz, $CDCl_3$): 0.97 (t, 3H, *J*=7.4 Hz, Me), 1.15 (d, 3H, *J*=6.9 Hz, Me), 1.43–1.52 (m, 1H, C**H**$_2$), 1.96–2.02 (m, 1H, C**H**$_2$), 3.24 (t, 1H, *J*=6.8 Hz, C*H*), 3.65 (quint., 1H, *J*=6.2 Hz, C*H*Me), 4.88 (bs, 1H, NH), 6.53 (d, 1H, *J*=8.17 Hz, ArH), 6.69 (t, 1H, *J*=7.4 Hz, ArH), 7.16 (bs, 1H, NH), 7.40 (t, 1H, *J*=7.0 Hz, ArH), 7.96 (d, 1H, *J*=8.0 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 10.9 (CH_3), 16.7 (CH_3), 24.0 (CH_2), 50.6 (CH), 62.5 (CH), 117.5 (CH), 118.0 (CH), 124.0 (quat.), 132.7 (CH), 133.2 (CH), 145.5 (quat.), 169.5 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3341, 3155, 2960, 2926, 2855, 1626, 1464, 1262, 1216, 1088, 1022, 668. EI mass spectrum (*m*/*z*, %): 205 (MH^+, 10%), 204 (65%), 189 (15%), 175 (20%), 161 (55%), 147 (30%), 133 (90%), 132 (100%), 118 (30%), 104 (75%), 77 (40%), 57 (35%), 44 (40%). HRMS (ES+): found MH^+ 205.1339, $C_{12}H_{16}N_2O$ requires MH^+ 205.1341.

4.5.3. 1,2,3,4-Tetrahydro-2-isopropyl-1,4-benzodiazepin-5-one 9c. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.0239 g, 29%) from 2-methyl-4-(*o*-nitrobenzamido)-but-1-en-3-one **7c** (0.1000 g, 0.4028 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 0.90 (d, 3H, *J*=6.8 Hz, Me), 0.96 (d, 3H, *J*=6.7 Hz, Me), 1.81 (octet, 1H, *J*=6.6 Hz, CHC*H*Me_2), 3.27 (dd, 1H, *J*=5.8, 1.9 Hz, C*H*$_2$), 3.28–3.36 (m, 2H, C*H*$_2$ and C*H*CHMe_2), 6.55 (d, 1H, *J*=8.2 Hz, ArH), 6.75 (t, 1H, *J*=7.5 Hz, ArH), 7.16 (dd, 1H, *J*=6.9, 1.6 Hz, ArH), 7.29 (bs, 1H, NH), 7.49 (d, 1H, *J*=7.3 Hz, ArH), 7.79 (dd, 1H, *J*=6.5, 1.5 Hz, ArH), 8.03 (dd, 1H, *J*=7.1, 1.5 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 18.3 (CH_3). 18.9 (CH_3), 29.7 (CH), 42.8 (CH_2), 65.0 (CH), 118.2 (CH), 118.9 (CH), 128.3 (quat.), 132.5 (CH), 132.9 (CH), 145.1 (quat.), 172.1 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3328, 3166, 2963, 2927, 1637, 1609, 1466, 1264, 1098, 1047, 796. EI mass spectrum (*m*/*z*, %): 205 (MH^+, 5%), 204 (20%), 161 (60%), 133 (45%), 132 (40%), 84 (100%), 104 (20%), 91 (40%), 77 (40%), 57 (45%), 49 (85%). HRMS (ES+): found MH^+ 205.1338, $C_{12}H_{16}N_2O$ requires MH^+ 205.1341.

4.5.4. 2-Ethyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5-one 9d. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.0325 g, 40%) from 4-(*o*-nitrobenzamido)-but-1-en-3-one **7d** (0.1000 g, 0.4270 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.10 (t, 3H, *J*=7.4 Hz, Me), 1.60

(hextet, 1H, J=7.3 Hz, CHCH_2Me), 2.00–2.05 (m, 1H, J=7.2 Hz, CHCH_2Me), 3.24–3.35 (m, 1H, CHN), 3.40 (dd, 1H, J=5.7, 2.3 Hz, CH_2N), 3.57 (dd, 1H, J=6.6, 2.3 Hz, CH_2N), 4.95 (bs, 1H, NH), 6.60 (d, 1H, J=8.2 Hz, NH), 6.81 (t, 1H, J=7.5 Hz, ArH), 7.41 (d, 1H, J=7.5 Hz, ArH), 7.91 (dd, 1H, J=7.8, 1.6 Hz, ArH), 8.10 (dd, 1H, J=7.2, 1.3 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 14.1 (CH_3), 22.7 (CH_2), 31.9 (CH_2), 44.9 (CH), 118.7 (CH), 119.3 (CH), 128.1 (CH), 129.7 (quat.), 132.9 (CH), 139.8 (quat.), 161.9 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3307, 3149, 2966, 2925, 1633, 1444, 1260, 1096, 1035, 798, 698. EI mass spectrum (*m/z*, %): 191 (MH^+, 10%), 190 (75%), 161 (100%), 133 (55%), 132 (80%), 118 (20%), 104 (45%), 77 (35%), 57 (25%). HRMS (ES+): found MH^+ 191.1188, $C_{11}H_{14}N_2O$ requires MH^+ 191.1184.

4.5.5. 2,3,4,5-Tetrahydro-4-hydroxy-3-methyl-4-(*n*-propyl)-1,2,5-benzothiadiazepin-1,1-dioxide 14. Obtained, as a single spot by TLC, by the identical procedure via column chromatography (eluent PE:EtOAc, 1:1) as a yellow oil (0.0408 g, 45%) from (*E*)-5-(*o*-nitrobenzenesulfamido)-hex-2-en-4-one **13** (0.1000 g, 0.3352 mmol, 1 equiv.).

δ_H (400 MHz, $CDCl_3$): 0.76 (t, 3H, J=7.4 Hz, Me), 1.30 (d, 3H, J=7.2 Hz, Me), 1.42 (hextet, 2H, J=7.4 Hz, CH_2CH_2Me), 2.18 (dt, 1H, J=17.4, 7.1 Hz, CH_2CH_2Me), 2.37 (dt, 1H, J=17.6, 7.0 Hz, CH_2CH_2Me), 3.88 (quintet, 1H, J=7.1 Hz, CHMe), 4.89 (bs, 2H, OH and NH), 5.89 (d, 1H, J=6.8 Hz, NH), 6.71–6.80 (m, 2H, 2×ArH), 7.30 (t, 1H, J=7.4 Hz, ArH), 7.66 (d, 1H, J=7.9 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 13.4 (CH_3), 16.8 (CH_3), 19.0 (CH_2), 29.1 (CH), 40.9 (CH_2), 57.0 (quat.), 117.7 (CH), 118.0 (CH), 127.3 (quat.), 127.5 (quat.), 129.3 (CH), 134.3 (CH). υ_{max} (NaCl plates, neat, cm^{-1}): 3401, 3377, 3265, 3038, 2960, 1600, 1483, 1455, 1332, 1156, 1024, 753. EI mass spectrum (*m/z*, %): 271 (MH^+, 20%), 270 (95%), 199 (80%), 182 (50%), 156 (75%), 108 (35%), 92 (100%), 65 (40%). HRMS (CI+[NH_3]): found MNH_4^+ 288.1379, $C_{12}H_{18}N_2O_3S$ requires 288.1381.

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