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Competitive 1,3-Dipolar Cycloaddition Reactions of an Azomethine Ylide with Aromatic and Carbonyl Groups of Nitro-Substituted Isatoic Anhydrides

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Competitive 1,3-dipolar cycloaddition reactions of an azomethine ylide with aromatic and carbonyl groups of nitro-substituted isatoic anhydrides

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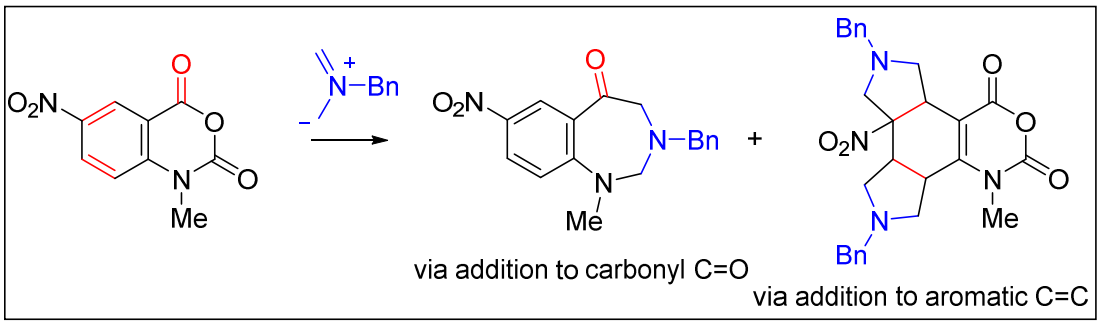
Table of Contents/Abstract Graphic



Abstract

A study of the reactivity of a non-stabilised azomethine ylide, derived from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine, with nitro-substituted isatoic anhydrides was undertaken. *N*-methyl-4-nitroisatoic anhydride underwent a 1,3-dipolar cycloaddition reaction exclusively at the isatoic anhydride C1-carbonyl group, followed by decarboxylative rearrangement to yield a benzo-1,3-diazepin-5-one derivative. In contrast, *N*-

methyl-5-nitroisatoic anhydride underwent competing cycloaddition processes, to the isatoic anhydride C1-carbonyl group and to the nitro-substituted aromatic ring. The dearomative addition reaction resulted in the formation of novel tetracyclic products.

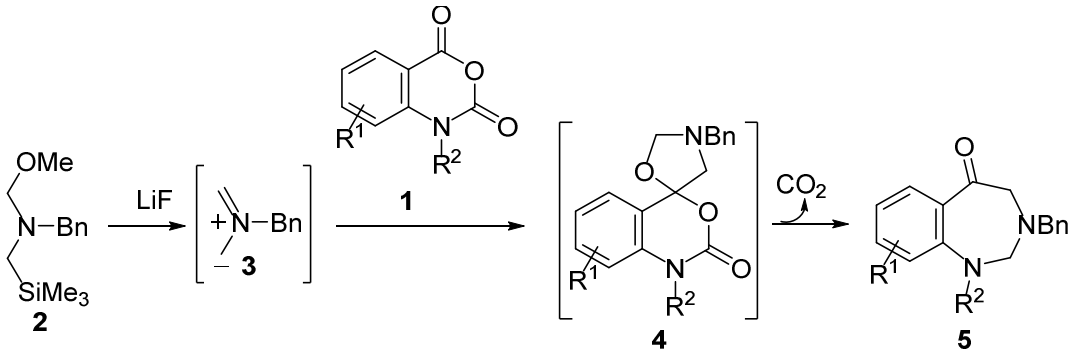
Introduction

There is significant interest in the field of organic synthesis in processes that result in dearomatisation of aromatic ring systems, due in part to the ready availability of aromatic building blocks and in part to the challenge of functionalization of relatively stable aromatic systems.[1,2] The process of dearomative cycloaddition to aromatic systems serves to introduce a higher degree of complexity into the products; pertinent examples including the photo-induced intramolecular cycloaddition of aza-ortho-xylylenes,[3] intramolecular [4 + 2]-cycloadditions of allenes to arenes,[4] of dienes to benzofurans[5] and to indoles,[6-8] of 1,3,4-oxadiazoles to indoles,[9] as well as intermolecular [3 + 2]-cycloaddition reactions of carbonyl ylides and indoles,[10] and of trimethylenemethanes with nitroarenes.[11] Recent examples include intramolecular [4 + 3]-cycloaddition of arenes with epoxy and aziridinyl enolsilanes,[12] dearomative indole [5 + 2]-cycloaddition reactions,[13] [3 + 2]-annulations of aminocyclopropanes with electron poor six-membered *N*-heterocycles,[14] [3 + 2]- and [4 + 2]-annulations of 3-nitroindoles[15,16] and nickel-catalysed trans-1,2-carboamination.[17] Despite these advances, the 1,3-dipolar cycloaddition reactions of azomethine ylides with aromatic dipolarophiles has received scant attention.[18] The first example, reported by Huisgen and Scheer in 1970, involved addition of a stabilised azomethine ylide to polycyclic aromatic systems such as naphthalene and anthracene.[19] Later intramolecular cycloaddition reactions of azomethine ylides and benzenoid aromatic systems was reported under conditions of flash vacuum pyrolysis.[20] More recently, the propensity for nitrobenzene/nitroaromatic derivatives to undergo such reactions has been revealed.[21-24] As an extension to studies into the cycloaddition reactions of a non-stabilized azomethine ylide to carbonyl dipolarophiles,[25-28]

we now report the first example of a cycloaddition reaction to the aromatic ring of an isatoic anhydride derivative.

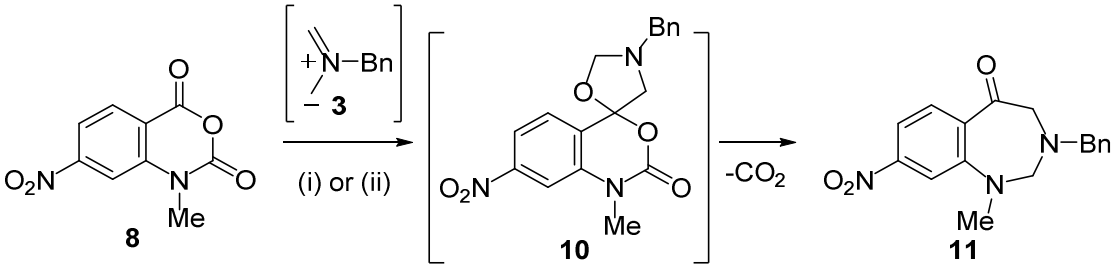
Results and Discussion

Previously, we found that a range of isatoic anhydride derivatives **1** (R^1= Cl, Br, Me, F, OMe, CO_2Me) undergo 1,3-dipolar cycloaddition reactions at the C1-carbonyl group with the non-stabilised azomethine ylide **3**, generated in situ by the lithium fluoride-promoted extrusion of trimethylsilylmethoxide from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**2**), to afford cycloadducts **4**.[26] The cycloadducts proved to be unstable under the reaction conditions and were found to spontaneously undergo oxazolidine ring opening–decarboxylation–7-endo-trig ring closure to afford benzo-1,3-diazepin-5-ones **5** (Scheme 1). We observed that electron-withdrawing substituents on the aromatic ring of the isatoic anhydrides resulted in more rapid conversions. In order to further explore the effects of electron-withdrawing substituents, *N*-methyl-4-nitro- and -5-nitro-isatoic anhydride (**8**)[29] and (**9**)[30] were prepared by *N*-methylation[26,31] of the respective parent nitroisatoic anhydride **6**[32] and **7**[33] (see Experimental section).



Scheme 1: Previous work: 1,3-Dipolar cycloaddition–decarboxylation reactions of non-stabilised azomethine ylide **3** with isatoic anhydrides **1**.[26]

The reaction of *N*-methyl-4-nitroisatoic anhydride (**8**) with azomethine ylide **3**, generated from reagent **2**, was explored using two methods for generating the ylide.[26] When the ylide was generated by treatment of reagent **2** with either lithium fluoride in acetonitrile or with catalytic amounts of trifluoroacetic acid in dichloromethane, the anticipated reaction occurred, presumably again via spiro cycloadduct **10**, to afford the corresponding nitro-substituted benzo-1,3-diazepin-5-one **11**, isolated after chromatographic purification in 62% and 83% yield respectively (Scheme 2).



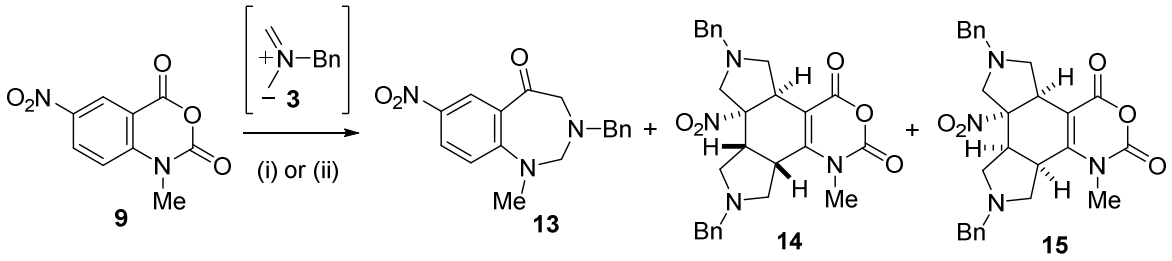
8 **10** **11**

Scheme 2. (i) **2**, LiF, 4 Å MS, CH_3CN, 35–40 °C, 3.5 h, 62%. (ii) **2**, CF_3CO_2H (0.05 equiv.), 3 Å MS, CH_2Cl_2, 0 °C to rt, 16 h, 83%.

In contrast to the outcome from the reaction of the 4-nitroisatoic anhydride **8** described above, the corresponding reaction of *N*-methyl-5-nitroisatoic anhydride (**9**) with azomethine ylide **3**, generated from reagent **2** and lithium fluoride in acetonitrile, resulted in a surprisingly low isolated yield of the expected benzo-1,3-diazepin-5-one **13** (Scheme 3). The experiment was repeated and analysis of the crude reaction mixture by TLC indicated full conversion of the starting material and the presence of a bright yellow spot due to the expected benzo-1,3-diazepin-5-one **13** as well as two colourless spots of higher R_F. Inspection of the ^{1}H NMR spectrum of the crude reaction mixture indicated signals in the aliphatic region that hitherto had not been observed in the previous reactions of azomethine ylide **3** with isatoic anhydrides.[26] The benzo-1,3-diazepin-5-one **13** was isolated in 7% yield and the major component of the two other products was isolated in 20% yield. MS analysis

indicated that the major component was a *bis* azomethine ylide adduct ($M^{+\cdot}$ = 488), meaning the yields were potentially limited by the amount of azomethine ylide reagent. The reaction was repeated on larger scale with more equivalents of azomethine ylide precursor (2.2 molar equivalents relative to **9**), followed by chromatography on silica gel, leading to isolation of the benzodiazepinone **13** (20%) and major *bis* adducts **14** (46%) and minor *bis* adduct **15** (8%) (Scheme 3). When the reaction was performed by generating the ylide **3** by the action of catalytic amounts of trifluoroacetic acid, similar yields of products were obtained (Scheme 3).

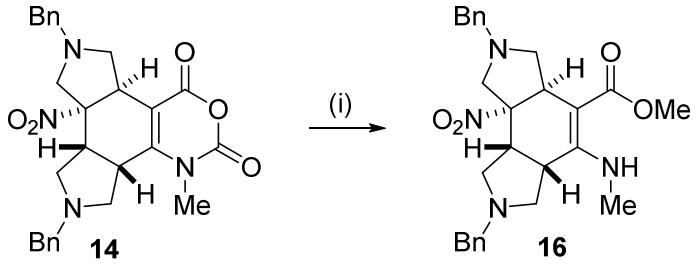
As mentioned, the MS data indicated that both unexpected products were *bis* adducts ($M^{+\cdot}$ = 488). The NMR and IR data indicated that, surprisingly, a two-fold addition had occurred to the aromatic ring of the nitro-substituted isatoic anhydride and that the anhydride ring was intact (e.g. IR $\nu_{C=O}$ = 1772 and 1715 cm^{-1} (major **14**); 1770 and 1712 cm^{-1} (minor **15**)). The major and minor components were assigned as the *anti bis* adduct **14** and *syn* bis adduct **15** respectively using a range of 2D NMR techniques (HSQC, HMBC and COSY) and this assignment was confirmed by determination of the X-ray crystal structure analysis of a derivative of the major *bis* adduct **14** (Figure 1).



Scheme 3. (i) **2**, 4 Å MS, CH_3CN, 35 °C, 3 h, **13** (20%), **14** (46%), **15** (8%). (ii) **2**, CF_3CO_2H (0.05 equiv.), 3 Å MS, CH_2Cl_2, 0 °C to rt, 16 h, **13** (23%), **14** (65%), **15** (7%).

Given the novel nature of the tetracyclic *bis* adducts, it was of interest to see whether the oxazinedione subunit of the major *bis* adduct **14** had retained the electrophilic character of the starting isatoic anhydrides. Although oxazinedione **14** did not react appreciably with

methanol, even on heating, in the presence of a catalytic amount of potassium carbonate at 40 °C a smooth ring-opening reaction occurred with concomitant decarboxylation to afford ester **16** as a crystalline solid, isolated in good yield (Scheme 4). The X-ray crystal structure of the product **16** clearly showed the *cis-anti-cis* relationship of the [5,6,5]-tricyclic ring system of the methyl ester **16**, and confirmed the earlier stereochemical assignment of the major *bis* adduct **14** and, by inference, the minor *bis* adduct **15** (Figure 1). The structure contains a vinylogous carbamate moiety defined by the atoms N4-C1-C2-C7-O2, and delocalisation of the p-type lone pair on N4 onto the carbonyl oxygen (O2) within this moiety is apparent from the bond distances; (N4-C2 1.348(2), C2-C1 1.379(2), C1-C7 1.445(2) and C7-O2 1.229(2) Å respectively. The resulting resonance enhanced intramolecular N-H…O hydrogen bond is characterised by the following parameters; N4···O2 2.685(2) Å, H···O2 1.98(2) Å, N4-H···O2 137(2)°. The structure forms dimeric units arranged around a crystallographic inversion centre characterised by N-H…O interactions N4···O2(i) 3.309(2), N4-H…O2(i) 134(2)° Å (Figure 1). The two vinylogous carbamate moieties are essentially coplanar (mean deviation 0.031 Å).



Scheme 4. (i) K_2CO_3, MeOH, 40 °C, 3 h, 73%.

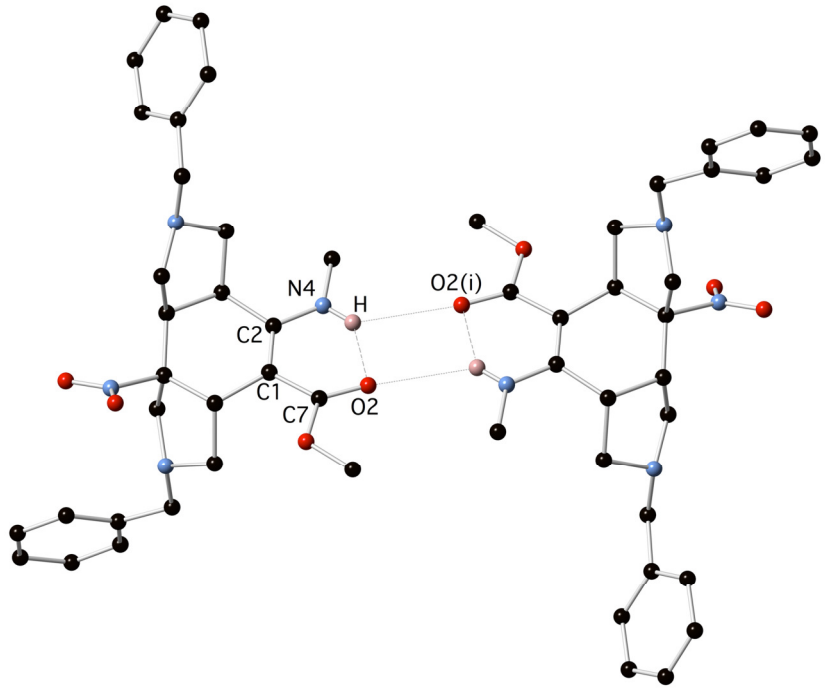
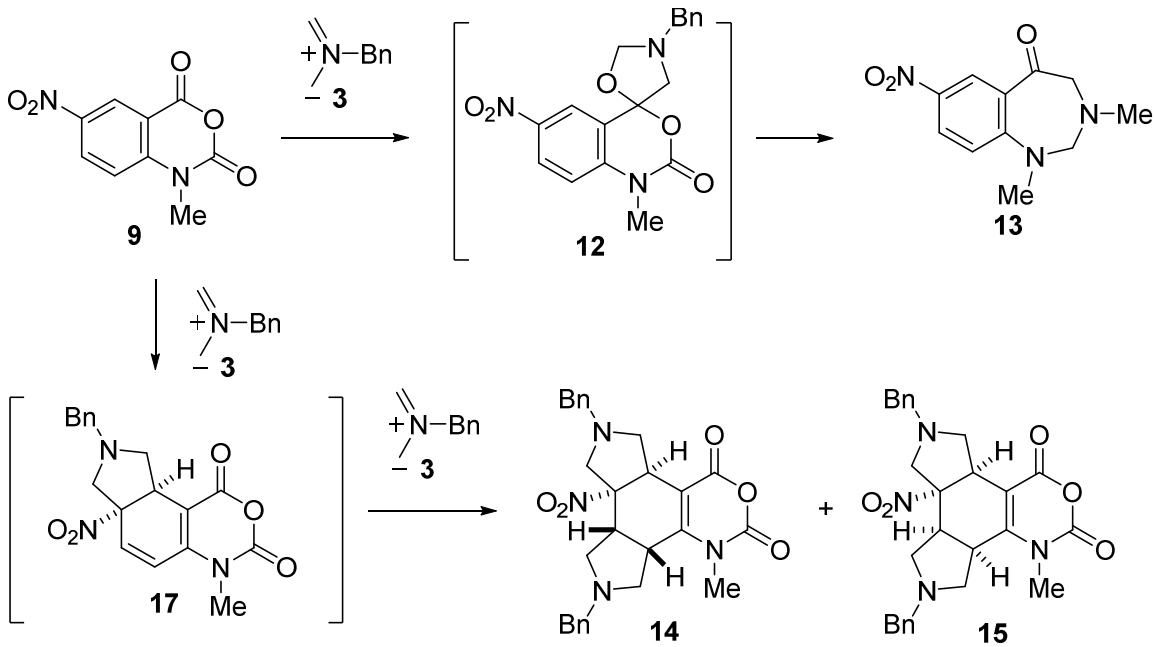


Figure 1. The dimeric units of compound **16**, held together by weak N-H…O interactions. Symmetry operator (i) 1-x, 1-y, 1-z.

Crystal data for **16**. $C_{27}H_{32}N_4O_4$, M = 476.56T = 130.0(2) K, λ = 1.54184 Å, Monoclinic, space group $P2_1/c$ a = 17.6227(2), b = 12.02730(10), c = 11.40730(10) Å, V = 2416.41(4) Å^3, Z = 4, D_c = 1.310 Mg M^{-3} μ(Cu-Kα) = 0.721 mm^{-1}, *F(000)* = 1016, crystal size 0.39 x 0.37 x 0.17 mm. θ_{max} = 73.27°, 11361 reflections measured, 4724 independent reflections (R_{int} = 0.41) the final R = 0.0453 [I > 2σ(I), 3801 data] and *w*R(F^2) = 0.125 (all data) GOOF = 1.049.

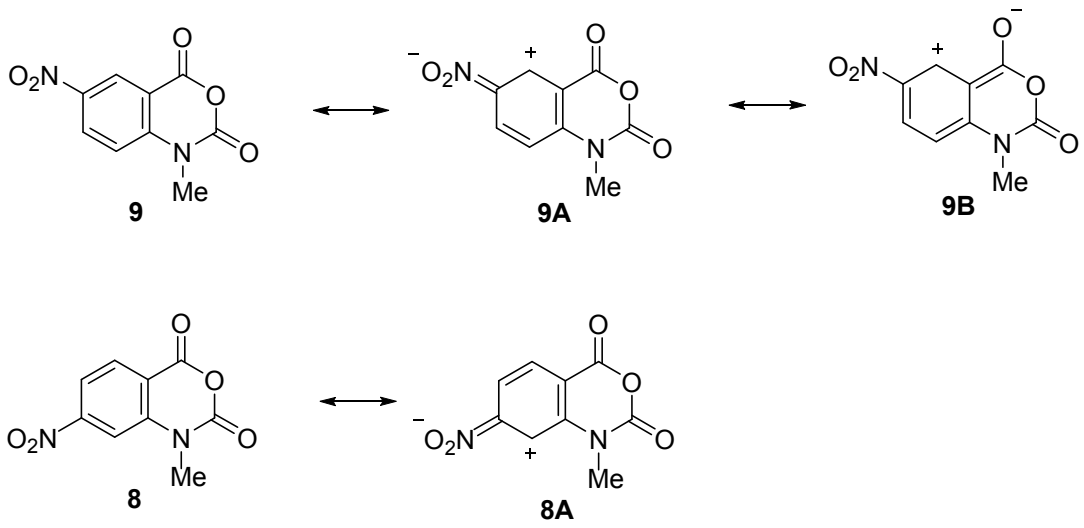
The 1,5-benzodiazepin-3-one **13** and *bis* adducts **14/15** are proposed to form by cycloaddition of the azomethine ylide **3** to either the anhydride carbonyl group or the aromatic ring of the nitro substituted isatoic anhydride **9** (Scheme 5).The addition of the ylide **2** to the carbonyl group of isatoic anhydride **9** would afford spiro-oxazolidine **12**, that would undergo a previously described ring-opening–decarboxylation–ring-closing reaction[26] to afford benzodiazepinone **13**. The addition of the ylide **2** to the aromatic system is thought to

be step-wise. The first addition is proposed to occur to the C5-C6 double bond because of the activation of this bond by both the nitro and isatoic anhydride carbonyl electron-withdrawing groups, yielding proposed mono adduct **17**. Apparently, the C5-C6 double bond of **9** is activated to the extent that cycloaddition to the C5-C6 double bond is somewhat faster than cycloaddition to the anhydride carbonyl group. The proposed *mono* adduct **17** was not isolated and, given the good mass balance of the isolated products, this indicates that **17** undergoes a very rapid and selective second cycloaddition, leading to the isolated *anti*- and *syn*- *bis* adducts **14** and **15** –this is expected, given that it is the first cycloaddition that disrupts the aromatic system. The observation that the *anti* adduct **14** is the major *bis* adduct can be accounted for by steric effects, with the second azomethine ylide addition favouring approach of the ylide to the less-hindered convex face of the *mono* adduct olefin. The observation that the internal C1-C2 carbon-carbon double bond of **17** does not react with the azomethine ylide could be due to a combination of stereoelectronic factors. The C3-C4 double bond is less hindered and also doesn't have an electron-donating group. Similar factors could be responsible for the lack of reactivity for the C1-C2 bond of starting material **9**. We and others have previously noted the sensitivity of azomethine ylide cycloadditions to stereoelectonic effects.[23-27]



Scheme 5. Proposed pathway for formation of **13**, **14** and **15** from **9**.

The observed different reactivity of the azomethine ylide towards nitroisatoic anhydrides **8** and **9** can be explained qualitatively by consideration of frontier molecular orbitals, in particular, resonance effects on dipolarophile LUMO co-efficients. In such normal electron-demand cycloaddition processes, reaction rates increase with higher LUMO co-efficients. For **9**, resonance effects can occur for both the nitro group and the anhydride carbonyl group, serving to increase the LUMO co-efficient at C6 (Scheme 6). In comparison, for **8**, resonance stabilising effects are limited to the nitro group, in turn limiting the LUMO co-efficient at C3. We propose that the enhanced resonance effects of **9** leads to a sufficiently high LUMO coefficient for the observed cycloaddition dearomatisation process to occur faster that cycloaddition to the isatoic anhydride carbonyl group.



Scheme 6. Major resonance effects on **8** and **9**.

Conclusion

In conclusion, to the best of our knowledge, this is the first report of a cycloaddition reaction to the aromatic ring of an isatoic anhydride derivative. The reaction produces structurally complex products that contain a number of functionalities suitable for further manipulation. We believe there is considerable opportunity for further exploration of the scope of this chemical process and in application of the novel products in bioactive discovery.

Experimental

(a) Synthesis

General Experimental Methods

Analytical thin layer chromatography (TLC) was conducted on Merck Kieselgel 60 F254 aluminium sheets and were visualised using a 254 nm ultraviolet lamp and/or by dipping in aqueous potassium permanganate. Melting points were recorded on an Electrothermal IA9300 digital melting point apparatus and are uncorrected. Elemental analyses were performed by Campbell Microanalytical Laboratory, University of Otago, Dunedin, New Zealand. Infrared spectra were recorded on Perkin Elmer 842 or SPECTRUM 2000 FT

183 infrared spectrometers. NMR experiments were performed on Bruker Avance 200, 400 and
184 500 MHz NMR spectrometers. NMR experiments were performed with the sample held at
185 25±0.1 °C for routine analysis. Chemical shifts for all experiments are referenced using the
186 Unified Scale relative to 0.3% tetramethylsilane in deuteriochloroform.[34,35] Samples for NMR
187 spectroscopy were prepared by dissolving the analyte in deuterated solvent, as specified, and
188 placing the solution into a 5 mm NMR tube. The data were processed using Bruker TopSpin
189 v3.5 software. Positive ion electron impact (EI) mass spectra were run on a ThermoQuest
190 MAT95XL mass spectrometer using ionization energy of 70 eV. Accurate mass
191 measurements were obtained on the same instrument with a resolution of 5000-10000 using
192 perfluorokerosene (PFK) as the reference compound. Positive and negative ion electrospray
193 (ES) mass spectra were acquired with a VG Platform mass spectrometer using a cone voltage
194 of 50 V and the source was maintained at 80 °C. The solvent system used was acetonitrile
195 with a flow rate of 0.04 mL min^{-1}. Positive and negative ion atmospheric pressure on
196 chemical ionization (APCI) mass spectra were acquired with a VG Platform mass
197 spectrometer using a cone voltage of 50 V, and the source was maintained at 100 °C.
198 Nitrogen was used as the nebuliser and sheath gas, and the probe temperature was 400 °C.
199 The solvent system used was acetonitrile with a flow rate of 0.3 mL min^{-1}.

200 HPLC analyses were performed on a Waters Acquity UPLC comprising Sample Manager,
201 Binary Solvent Manager and Photodiode Array Detector using a 50x2.1mm BEH C18
202 column at 30 °C, scanning 190–500 nm measuring at 259 nm using the Empower data
203 management system. The mobile phase was 60% MeOH in water with 0.1% trifluoroacetic
204 acid (isocratic) and the flow rate was 0.4 mL min^{-1}.

205 All reactions were carried out under an inert nitrogen atmosphere at 25 °C unless otherwise
206 stated. Glassware for inert atmosphere reactions was oven-dried and cooled under a flow of
207 nitrogen. Hexanes refer to the fraction with boiling point 40–60 °C. Dry CH_3CN, DMF and

THF were obtained by passing the respective solvent through activated alumina columns and were stored over 4 Å molecular sieves. All starting materials, reagents and solvents were obtained from commercial sources and used as supplied unless otherwise noted. Flash chromatography was conducted according to the method of Still[35] using normal phase silica gel and analytical grade solvents.

Preparation of N-*methylated isatoic anhydrides **8** and **9**.*

4-Nitroisatoic anhydride (**6**)[32] was obtained from commercial sources or was prepared by the reaction of 4-nitroanthranilic acid with triphosgene in THF.[26] 5-Nitroisatoic anhydride (**7**)[33] was obtained from commercial sources or by nitration of isatoic anhydride with sodium nitrate in sulfuric acid.[35]

N-Methyl-4-nitroisatoic anhydride (**8**)[27] and *N*-methyl-5-nitroisatoic anhydride (**9**)[28] were prepared by the reaction of the respective nitroisatoic anhydride **6** or **7** with methyl iodide and sodium hydride in dimethylformamide,[26,33] or more conveniently with methyl iodide and diisopropylethylamine in dimethylformamide.[31]

*3-Benzyl-1-methyl-8-nitro-1,2,3,4-tetrahydro-5*H-*benzo[*d*][1,3]diazepin-5-one **11***

Method A. A mixture containing *N*-methyl-4-nitroisatoic anhydride (**8**) (0.149 g, 0.67 mmol), *N*-(methoxymethyl)-*N*-(trimethylsilyl)benzylamine (**2**) (0.46 mL, 0.42 g, 1.8 mmol), lithium fluoride (0.033 mg, 1.25 mmol) and powdered 4 Å molecular sieves (0.200 g) in acetonitrile (3 mL) was sonicated at 35–40 °C under an atmosphere of nitrogen for 3.5 h. The mixture was filtered through a plug of silica, then concentrated to give the crude product. The crude product was subjected to flash chromatography (silica, 1:5 EtOAc: petroleum spirits) to afford after concentration of the fractions (R_F 0.4) the *title compound* **11** (0.130 g, 62%) as a yellow solid, mp 121–122 °C. ν_{max} (KBr)/cm^{-1} 1667, 1610, 1526, 1441, 1414, 1352, 1318,

1274, 1198, 1068, 983, 883, 699. δ_H (200 MHz, $CDCl_3$) 7.91 (d, *J* 8.6, 1H), 7.73 (d, *J* 2.0, 1H), 7.63 (dd, *J* 8.6 and 2.0, 1H), 7.39–7.30 (m, 5H), 4.16 (s, 2H), 3.88 (s, 2H), 3.57 (s, 2H), 3.24 (s, 3H). δ_C (50 MHz, $CDCl_3$) 197.6, 153.0, 150.6, 137.1, 131.4, 130.3, 128.9, 128.7, 127.8, 112.5, 108.6, 76.4, 64.1, 58.5, 40.1. *m/z* (EI) 311 (43%, $[M-H]^+$), 220 (11), 192 (38), 191 (100), 136 (33), 91 (64). HRMS *m/z* (EI) Calc'd for $C_{17}H_{17}N_3O_3$ $[M-H]^+$: 311.1270. Found 311.1260. Anal. Calcd for $C_{17}H_{17}N_3O_3$: C 65.58, H 5.50, N 13.50. Found: C 65.57, H 5.52, N 13.64.

Method B. A mixture of *N*-methyl-4-nitroisatoic anhydride (**8**) (0.051 g, 0.23 mmol), *N*-(methoxymethyl)-*N*-(trimethylsilyl)benzylamine (0.094 g, 0.39 mmol) and powdered 4 Å molecular sieves (0.025 g) in anhydrous CH_2Cl_2 (1 mL) was cooled to 0 °C under nitrogen. To this mixture was added trifluoroacetic acid (0.11 mL, 0.1 M in CH_2Cl_2, 0.01 mmol). The reaction mixture was then allowed to warm to room temperature and stirred at room temperature for 15 h, after which time TLC analysis indicated the reaction had gone to completion. The reaction mixture was concentrated under reduced pressure(bath temperature < 40 °C). The crude product was then subjected to flash chromatography to afford the *title compound* **11** (0.059 g, 83%) as a yellow solid. This material displayed identical IR and ^{1}H and ^{13}C NMR spectra to material obtained by Method A.

*3-Benzyl-1-methyl-7-nitro-3,4-dihydro-1*H*-benzo[1,3]diazepin-5(2*H*)-one* ***13****, (4β*R*,7α*S*,7β*R*,10α*S*)-6,9-dibenzyl-1-methyl-7α-nitro-4β,5,6,7,7α,7β,8,9,10,10α-decahydro-2*H*-[1,3]oxazino[4,5-*e*]pyrrolo[3,4-*g*]isoindole-2,4(1*H*)-dione* ***14*** *and (4β*R*,7α*S*,7β*S*,10α*R*)-6,9-dibenzyl-1-methyl-7α-nitro-4β,5,6,7,7α,7β,8,9,10,10α-decahydro-2*H*-[1,3]oxazino[4,5-*e*]pyrrolo[3,4-*g*]isoindole-2,4(1*H*)-dione* ***15***

Method A. A mixture containing 5-nitro-*N*-methylisatoic anhydride (**9**) (1.11 g, 5.0 mmol), *N*-(methoxymethyl)-*N*-(trimethylsilyl) benzylamine **2** (2.61 g, 2.81 mL, 11.0 mmol), LiF (0.163

g, 6.25 mmol) and powdered 4 Å molecular sieves (1.0 g) in CH_3CN (20 mL) was sonicated at 35–40 °C under an atmosphere of nitrogen gas for 3 h. The resulting mixture was filtered and the solvent removed under *vacuo.* The crude product was subjected to flash chromatography (silica, gradient 0:100–100:0 EtOAc: petroleum ether). Concentration of the fractions (R_F 0.5, 1:1 EtOAc: petroleum ether) afforded the *title compound* **13** (303 mg, 20%) as a yellow solid. ν_{max} (KBr)/cm^{-1} 3096, 3062, 2957, 2910, 2821, 1675, 1598, 1573, 1506, 1491, 1451, 1423, 1386, 1324, 1289, 1266, 1255, 1196, 1165, 1151, 1112, 1081, 1151, 1112, 1081, 1067, 1015, 987, 928, 869, 824, 776, 744, 700, 645, 597, 519, 474. δ_H (200 MHz, $CDCl_3$) 8.70 (d, *J* 2.8, 1H), 8.21 (dd, *J* 2.8 and 9.4, 1H), 7.36–7.33 (m, 5H), 6.89 (d, *J* 9.4, 1H), 4.24 (s, 2H), 3.89 (s, 2H), 3.62 (s, 2H), 3.24 (s, 3H). δ_C (50 MHz, $CDCl_3$) 196.5, 156.1, 139.1, 128.9, 128.8, 128.0, 127.9, 127.3, 125.2, 113.4, 75.8, 64.3, 58.4, 40.4 (one signal obscured). *m/z* (EI) 311 (38%, $[M-H]^+$), 220 (11), 191 (100), 136 (12), 91 (48). HRMS *m/z* (EI) Calc'd for $C_{17}H_{17}N_3O_3$ $[M-H]^+$ 311.1264. Found 311.1267. Concentration of the fractions (R_F 0.3, 1:1 EtOAc: petroleum ether) afforded the *title compound* **15** (0.193 g, 8%) as a white fluffy solid, mp 161–164 °C. ν_{max} (KBr)/cm^{-1} 3027, 2924, 2813, 1770, 1712, 1643, 1541, 1493, 1469, 1453, 1436, 1348, 1312, 1208, 1138, 1118, 1075, 1028, 754, 700. δ_H (500 MHz, $CDCl_3$) 7.36–7.26 (m, 6H), 7.24–7.18 (m, 4H), 4.11 (dd, *J* 8.0 and 6.0, 1H), 3.75 (d, *J* 12.0, 1H), 3.68 (d, *J* 8.0, 1H), 3.63–3.48 (m, 4H), 3.38 (m, 1H), 3.31 (s, 3H, NCH_3), 3.24 (m, 1H), 3.15 (m, 1H), 2.98 (m, 2H), 2.88 (m, 1H), 2.63 (m, 1H), 2.54 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3, 152.1, 148.7, 137.6, 128.7 (2), 128.6 (2), 128.5, 127.7, 127.5, 104.7, 93.8, 59.6, 59.4, 59.2, 58.6, 57.3, 55.6, 43.5, 40.0, 38.3, 33.4 (N-$\underline{C}H_3$) (one signal obscured). *m/z* (ES+) 489.3 (70%, $[M+H]^+$), 438.3 (18), 398.4 (20), 336.3 (20), 251.3 (19), 220.2 (41), 134.2 (100). HRMS *m/z* (ES+) Calc'd for $C_{27}H_{28}N_4O_5$ $[M+H]^+$ 489.2132. Found $[M+H]^+$ 489.2138. Anal. Calc'd for $C_{27}H_{28}N_4O_5$: C 66.38, H 5.78, N 11.47. Found: C 66.27, H 5.77, N 11.44. Concentration of the fractions (R_F 0.2, 1:1 EtOAc: petroleum ether) afforded the *title*

compound **14** (1.13 g, 46%) as a buff-coloured fluffy solid, mp 92–97 °C. ν_{max} (KBr)/cm^{-1} 3028, 2959, 2919, 2806, 1772, 1715, 1640, 1543, 1453, 1434, 1353, 1334, 1312, 1144, 1084, 1029, 752, 701. δ_H (500 MHz, $CDCl_3$) 7.33–7.28 (m, 6H), 7.26–7.19 (m, 4H), 3.96 (dd, *J* 9.0 and 9.0, 1H), 3.67 (d, *J* 13.5, 1H), 3.59 (d, *J* 13.0, 1H), 3.54 (d, *J* 13.0, 1H), 3.37 (d, *J* 10.5, 1H), 3.35–3.34 (m, 2H), 3.28 (s, NCH_3), 3.24–3.20 (m, 1H), 3.05 (t, *J* 10.0, 1H), 2.99 (d, *J* 10.0, 1H), 2.88 (dd, *J* 9.8 and 4.9, 1H), 2.76 (dd, *J* 9.8 and 6.0, 1H), 2.64 (t, *J* 9.5, 1H), 2.64 (d, *J* 9.0, 1H) δ_C (126 MHz, $CDCl_3$) 158.4, 152.1, 148.7, 137.4, 137.2, 128.5, 128.5, 128.4, 127.5, 105.6, 91.7, 60.7, 59.2, 58.8, 58.4, 56.6, 54.4, 42.5, 38.4, 38.4, 33.3 (one signal obscured). *m/z* (ES+) 489.2 (90%, $[M+H]^+$). Anal. Calc'd for $C_{27}H_{28}N_4O_5$: C 66.38, H 5.78, N 11.47. Found: C 66.65, H 5.95, N 11.45.

Method B. A mixture of *N*-methyl-5-nitroisatoic anhydride (**9**) (0.050 g, 0.23 mmol), *N*-(methoxymethyl)-*N*-(trimethylsilyl)benzylamine (0.109 g, 0.46 mmol) and powdered 3 Å molecular sieves (0.050 g) in anhydrous CH_2Cl_2 (1 mL) was cooled to 0 °C under nitrogen. To this mixture was added trifluoroacetic acid (0.12 mL, 0.1 M in CH_2Cl_2, 0.01 mmol). The reaction mixture was then allowed to warm to room temperature and stirred at room temperature for 16 h, after which time TLC analysis indicated the reaction had gone to completion. The reaction mixture was concentrated under reduced pressure(bath temperature < 40 °C). The crude product was then subjected to flash chromatography to afford *title compound* **13** (0.016 g, 23%), as a yellow solid, *title compound* **15** (0.007 g, 7%) as an off-white solid, and *title compound* **14** (0.030 g, 28%) as an off-white solid. These materials displayed identical ^{1}H NMR spectra to the materials obtained by Method A.

Methyl (3aR,5aS,8aR,8bS)-2,7-dibenzyl-5-(methylamino)-8b-nitro-1,2,3,3a,5a,6,7,8,8a,8b-decahydropyrrolo[3,4-e]isoindole-4-carboxylate ***16***

The major *bis adduct* **14** (0.12 g, 0.25 mmol) was dissolved in MeOH (2.5 mL). To this solutions was added potassium carbonate (0.017 g, 0.12 mmol) was added and the mixture stirred at 40 °C for 3 h over which time a white solid separated. TLC analysis of the reaction mixture showed traces of starting material. The mixture was stored at 4 °C for 12 h then concentrated under vacuum. The residue was dissolved in EtOAc, washed with water, dried ($MgSO_4$) and concentrated to give the crude product which was subjected to flash column chromatography (silica, 3: 7 EtOAc: petroleum ether). Concentration of the fractions (R_F 0.4, 1:1 EtOAc: petroleum ether) afforded the *title compound* **16** (0.086 g, 73%) as viscous golden coloured oil. Trituration of the oil with toluene afforded a buff coloured solid, 152–154 °C. ν_{max} (KBr)/cm^{-1} 3274, 3027, 2948, 2807, 1651, 1602, 1541, 1453, 1437, 1365, 1235, 1182, 1160, 1146, 1101, 1075, 1054, 1027, 908, 790, 742, 700, 465. δ_H (200 MHz, $CDCl_3$) 8.97 (q, *J* 5.4, 1H, -N<u>H</u>CH_3), 7.34–7.24 (m, 10H), 3.98 (dd, *J* 5.2 and 5.0, 1H), 3.66 (s, 3H, OC<u>H</u>$_3$), 3.66–3.46 (m, 4H), 3.36 (d, *J* 9.8, 1H), 3.36 (dd, *J* 5.0 and 4.8, 1H), 3.26–3.15 (m, 1H), 3.21 (m, 1H), 3.13 - 3.05 (m, 1H), 2.90 (d, *J* 10, 1H), 2.81 (d, *J* 5.4, 3H, -NH-C<u>H</u>$_3$), 2.73 (d, *J* 5.4, 2H), 2.56 (dd, *J* 9.0 and 8.0, 1H), 2.40 (dd, *J* 5.0 and 5.2, 1H). ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.3, 158.7, 138.3, 138.1, 128.5, 128.4, 128.3, 128.3, 127.2, 127.1, 93.5, 90.6, 62.4, 61.1, 59.7, 59.2, 58.1, 55.0, 50.7, 41.5, 38.7, 37.8, 30.3. Anal. Calc'd for $C_{27}H_{32}N_4O_4$: C 68.05, H 6.77, N 11.76. Found: C 66.94/67.22, H 7.01/7.00, N 11.45/11.41. Compound **16** was recrystallized by slow diffusion of pentane into a solution in benzene held at 25 °C for 3–4 weeks. The colourless crystalline masses that were obtained contained crystals that were suitable for X-ray crystallography analysis (see Supplementary Material).

(b) Crystallography

Intensity data were collected with an Oxford Diffraction XCalibur CCD diffractometer using Cu- Ka radiation, the temperature during data collection was maintained at 130.0(1) using an Oxford Cryosystems cooling device. The structure was solved by direct methods and

difference Fourier synthesis.[38] Thermal ellipsoid plots were generated using the program ORTEP-3[39] integrated within the WINGX[40] suite of programs.

Supplementary Material

^{1}H NMR and ^{13}C NMR spectra of all new compounds and X-ray crystallographic data for compound **16** are available on the Journal's website. The crystallographic information file (cif) for compound **16** has been deposited at the Cambridge Crystallographic Data Centre and assigned the CCDC code 1835145.

Conflicts of Interest

The authors declare no conflicts of interest.

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