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# Metal-free oxidative ring contraction of benzodiazepinones: an entry to quinoxalinones

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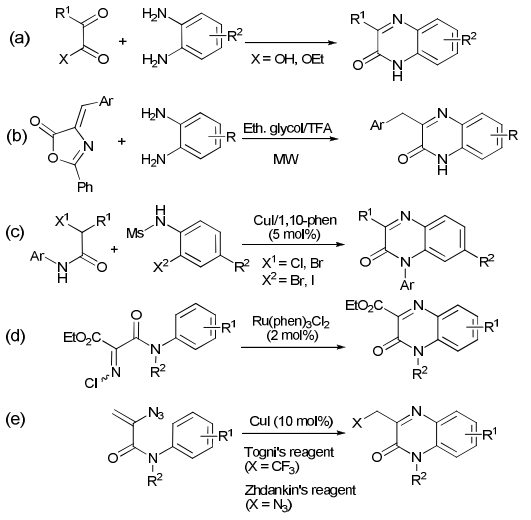
A novel and practical synthesis of 3-benzoylquinoxalin-2(1H)-ones from benzodiazepin-2-ones and in two steps from commercially available starting materials is reported. The reaction was achieved in the presence of N-bromosuccinimide in DMSO which served both as solvent and oxidant. Significantly, the yet unknown ketone to alcohol fluorescence turn-on of benzoylquinoxalinones was unveiled through the preparation of a fluorescently labelled cholesterol conjugate.

## Introduction

The nitrogen-containing heterocycle quinoxalin-2(1H)-one has undoubtedly become a privileged skeleton within the quinoxaline family.[1] Quinoxalinone derivatives exhibit an amazingly wide spectrum of biological properties including, among others, anticancer,[2] antimicrobial,[3] antithrombotic,[4] protein kinase inhibitory,[5] or benzodiazepine receptor agonist activity.[6] Importantly, they are also present in pharmaceutical compounds such as ataquimast,[7] an anti-inflammatory agent, or caroverine,[8] a spasmolytic drug. Besides, quinoxalinones are useful key synthetic intermediates for the construction of quinoxaline[9] or benzimidazolone[10] scaffolds. Furthermore, electronic properties of these heterocycles have been leveraged in free radical photoinitiated polymerization processes[11] and fluorescence applications.[12]

From the synthetic point of view, quinoxalinones are traditionally generated by condensation of *o*-phenylenediamines with α-keto acids or with their related derivatives,[13] in accordance with the method developed more than a century ago by Hinsberg (Scheme 1 a).[14] In a more elaborate approach, Jung *et coll.*, and Tu *et al*. reported the reaction of *o*-phenylenediamines with masked α-keto acid derivatives oxazolones, under microwave and solid support conditions, respectively (b).[15] Relatively few other approaches have been reported, most of them involving metal catalysis. In this context, Bao *et al*. reported copper-catalyzed domino $S_NAr$/coupling synthesis of quinoxalinones from N-phenyl sulfonamides and N-phenyl halo acetamides (c).[16] The cyclization of iminyl radicals generated either from *N*-chloroimines under visible light irradiation with $Ru(phen)_3Cl_2$ as photocatalyst (d) or from vinyl azides under copper catalysis (e), also constitute elegant approaches to quinoxalinone systems.[17]

Herein, we propose a complementary metal-free approach to the quinoxalinone core through an intramolecular oxidative rearrangement process of 1,5-benzodiazepin-2-ones. The fluorescence behavior of the 3-benzoylquinoxalin-2(1H)-one and its $NaBH_4$-reduced form was also explored. This strategy was subsequently applied to the preparation of a fluorescently labelled cholesterol derivative that would be suitable for imaging applications.




**Scheme 1** Previous work regarding the synthesis of quinoxalin-2(1H)-ones.

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†Electronic Supplementary Information (ESI) available: $^1H$, $^{13}C$ NMR, and photophysical data for all new compounds, X-ray crystallographic data (CIF files) for compound **2a** (CCDC 1519664). See DOI: 10.1039/x0xx00000x
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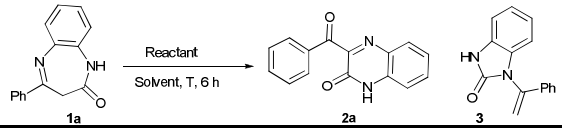
## Results and discussion

In the course of studies on the chemoselective acylation of 1,5-benzodiazepin-2-one derivatives, we unexpectedly observed the formation of the quinoxalin-2-one **2a**, albeit in a low yield of 15% (Table 1, entry 1). This structure was unequivocally established by X-ray crystallographic analysis (Fig. 1). In order to improve the efficiency of this transformation which involves an oxidation step, and a ring contraction step, the reaction was next carried out with one-electron oxidizing agents such as 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) or ceric ammonium nitrate (CAN). None of these conditions afforded the desired quinoxalinone **2a**. Alternatively, a protocol recently reported by Ravikumar for the oxidation of active methylenes using DMSO as sole oxidant in the presence of $Cs_2CO_3$ was also attempted.[18] No trace of compound **2a** was observed, but instead a [1,3] sigmatropic rearrangement proceeded resulting in the unexpected 1-(1-phenylvinyl)-1H-benzo[d]imidazol-2(3H)-one **3**,[19] which was obtained in 54% isolated yield.[20] Encouragingly, the reaction carried out with 40 mol % of *N*-bromosuccinimide (NBS) in DMSO at 80 °C led to **2a** in 29% yield (entry 5).[21] Increasing the reaction temperature to 110 °C enabled the formation of the quinoxalinone in an acceptable 52% yield (entry 6). It should be mentioned that the reaction could be conducted in dry or wet DMSO, under a degassed, argon atmosphere or under an open air system, without affecting the yield. In addition, the use of 20 mol % of NBS led to incomplete conversion, and a stoichiometric amount of NBS did not improve the efficiency of the reaction. Besides, NIS and NCS were both less efficient than NBS (entries 8-9).

**Table 1** Optimization study




| Entry | Reactant | Solvent | T (°C) | Convrsn (%)[a] | Yield (%)[a] 2 | 3 |
|---|---|---|---|---|---|---|
| 1 | AcCl (2 eq.) | DMSO | 80 | 100 | 15 | 0 |
| 2 | CAN (2 eq.) | ACN | 80 | 100 | 0 | 0 |
| 3 | DDQ (2 eq.) | ACN | 80 | 60 | 0 | 0 |
| 4 | $Cs_2CO_3$ (0.25 eq.) | DMSO | 125 | 100 | 0 | 54[b] |
| 5 | NBS (0.4 eq.) | DMSO | 80 | 40 | 29 | 0 |
| 6 | NBS (0.4 eq.) | DMSO | 110 | 100 | 52[b] | 0 |
| 7 | NBS (1 eq.) | DMSO | 110 | 100 | 62 | 0 |
| 8 | NCS (0.4 eq.) | DMSO | 110 | 45 | 9 | 0 |
| 9 | NIS (0.4 eq.) | DMSO | 110 | 100 | 30 | 0 |

[a] Unless specified, determined by $^1$H NMR of the crude reaction mixture relative to the internal standard 1-phenylcyclohexene. [b] Isolated yields.

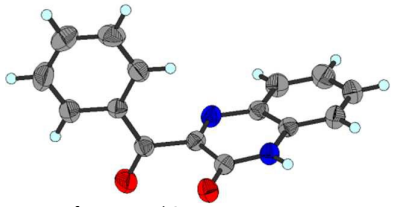
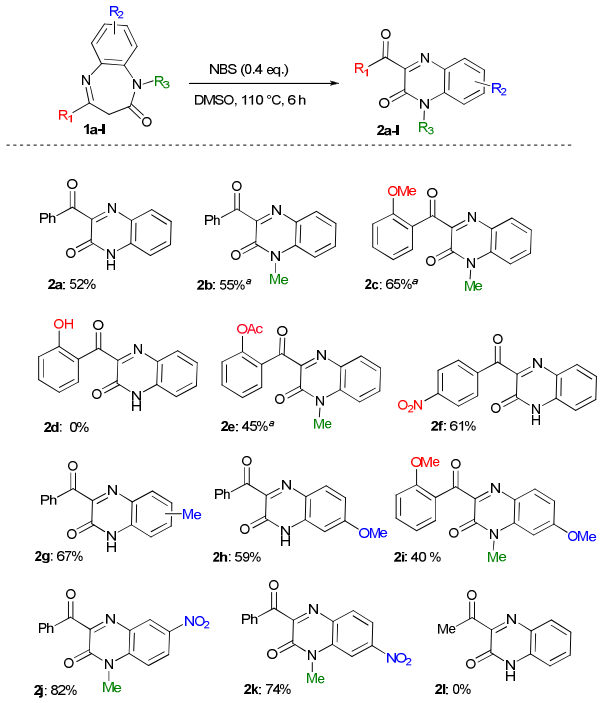


**Fig. 1** X-ray structure of compound **2a**.

Having established suitable reaction conditions (NBS 0.4 eq., DMSO, 110 °C), the scope of the transformation was next investigated with 1,5-benzodiazepin-2-ones **1a-l** differently substituted at positions $R^1$, $R^2$, and $R^3$. Results obtained are summarized in Scheme 2. First, substitution on the amide moiety with a methyl group was well tolerated. However, although reactions carried out with NH-free amides were completed within 6 h, some *N*-methyl amide derivatives have required longer reaction times (12 h, compounds **2b**, **2c**, **2e**). Satisfyingly, the optimized oxidizing process was compatible with benzodiazepin-2-ones bearing electron-rich phenyl rings. The products **2c**, **2h** and **2i** were obtained in convenient 65, 40 and 59% yield, respectively. Unfortunately, the phenol substrate failed to give the desired quinoxazolidinone **2d**, which could be attributed to the competitive bromination of the phenol ring. However, this limitation could be circumvented by protecting the hydroxyl group of the benzodiazepin-2-one into the corresponding phenyl acetate, which furnished compound **2e** in 45% yield. In addition, the ring contraction methodology was also effective with electron-withdrawing functions present either on the phenyl or on the fused aromatic ring system. In fact, nitro derivatives **2f**, **2j** and **2k** were obtained in good 61, 82 and 74% yield, respectively. Finally, when a substrate bearing a methyl group instead of a phenyl at $R^1$ was subject to the reaction conditions, only decomposition of the starting material was observed.




**Scheme 2** Scope of the oxidative ring contraction process of benzodiazepinones X-ray structure of compound **2a**. [a] Reaction time: 12 h.

A plausible reaction mechanism, depicted in Scheme 3a, was proposed on the basis of experimental data and results reported in the literature.[21, 22] Initially, electrophilic

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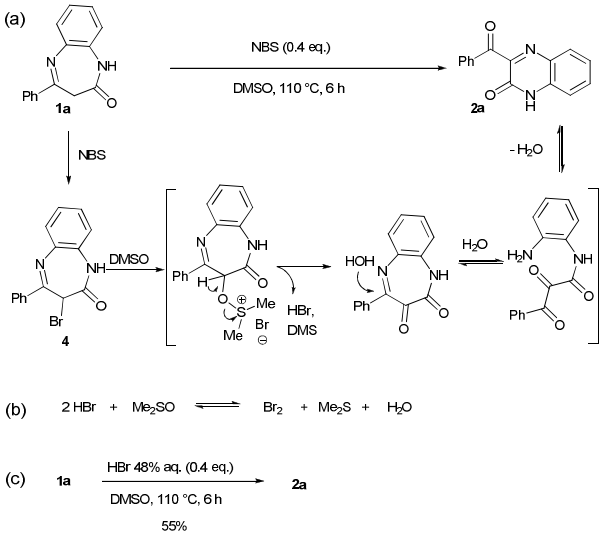
bromination at the C3 position of the benzodiazepinone by NBS would provide the corresponding alkyl bromide **4**, which may subsequently undergo the nucleophilic attack of DMSO. According to the Kornblum reaction,[23] the sulfonium thus formed would generate the α-keto amide with concomitant elimination of dimethyl sulfide (DMS) and hydrogen bromide (HBr). Finally, the thermodynamically driven 7-membered ring opening/ 6-membered ring closure process promoted by water would furnish the corresponding quinoxalinone **2a**. The water necessary at this stage, if not present initially, may result from the reaction of HBr with DMSO that would give rise to the formation of $H_2O$, DMS and $Br_2$ (Scheme 3b).[22, 24] Furthermore, *in situ* production of the $Br_2$ species (complexed with DMS) should contribute to making the system substoichiometric in bromonium source. In order to examine these mechanistic hypotheses, the reaction between the 1,5-benzodiazepinone **1a** and NBS was carried out in deuterated DMSO at room temperature. $^1$H NMR analysis of the reaction mixture showed that bromination of the methylene position was complete within the first minutes of reaction, which supports the first step of the mechanism (see Supporting Information). However, none of the other assumed intermediates, such as the sulfonium species, were identified.[25] Besides, in order to investigate whether the brominative species generated in the course of the reaction from HBr and DMSO may be able to perform the entire reaction sequence as assumed in the proposed mechanism, the synthesis of the quinoxalinone **2a** from 1,5-benzodiazepine **1a** was investigated using a 48% aqueous solution of HBr instead of NBS, in DMSO at 110 °C. Under these conditions, the quinoxalinone **2a** was indeed obtained, in 55% isolated yield (Scheme 3c). This experimental result thus supports the fact that a brominative species ($Br_2$) formed *in situ* may also be involved in the oxidative process involving NBS (40 mol %) and DMSO.




**Scheme 3** Proposed reaction mechanism.

To illustrate the potential of this synthetic methodology, the preparation of a fluorescently labelled cholesterol derivative was next investigated by using quinoxalinone scaffold as a fluorophore.[12] In fact, cholesterol is an essential component of cell membranes, which plays a critical role on membrane permeability and trafficking. Better understanding of the dynamics of cholesterol in membranes may require the preparation of fluorescent labelled cholesterol probes.[26] To do so, the covalent attachment of the cholesterol molecule to the fluorophore was first envisioned through the amide nitrogen of the quinoxalinone. However, our preliminary optical studies showed that quinoxalinone **2i**, an *N*-methylated model compound, has no significant fluorescence, whatever the excitation wavelength. In fact, few data are available on the fluorescence behavior of quinoxalinones,[12] hence we were surprised to notice that while compound **2i** was almost not fluorescent, its $NaBH_4$-reduced product **5** with a quantum yield of 0.11 (λem 475 nm upon an excitation at 366 nm in PBS 7.4 at 25 °C) was, in contrast, markedly more emissive (× 57, Fig. 2). To the best of our knowledge, this ketone-mediated quenching of fluorescence which might be explained through a singlet-triplet intersystem crossing process,[27] has never been reported with quinoxalinone derivatives. Besides, it is worth noting that the presence of the methoxy group at the C7 position on the quinoxalinone moiety was critical for fluorescence since the unsubstituted analog was not emissive, which is assumedly ascribed to the absence of a strong push-pull system.

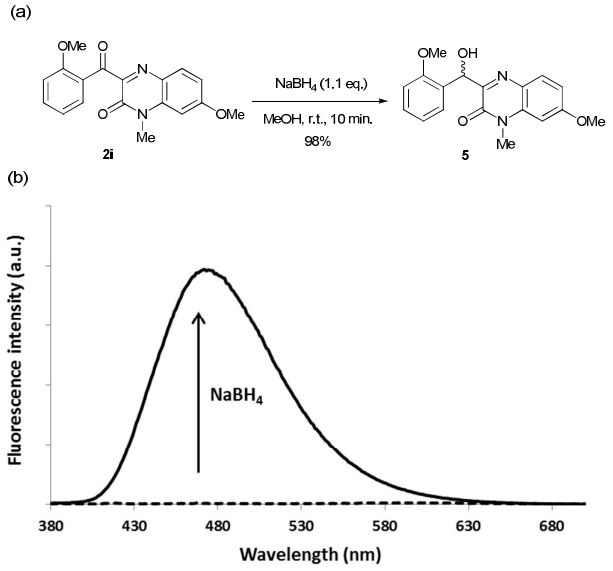



**Fig. 2** (a) Preparation of the hydroxyl-containing quinoxalinone **5**. (b) Fluorescence emission spectrum of quinoxalinone **2i** (λex 366 nm, λem 475 nm) in PBS 7.4 at 25 °C, before (dashed line) and after (black line) the addition of $NaBH_4$.

Following this unexpected result, we changed our strategy by taking advantage of the presence of the hydroxyl group to introduce a conjugatable handle which could subsequently be used to attach the sterol. This hydroxyl group thus formed in 98% yield was then used to install a propargyl function required for subsequent click chemistry with the azide partner **7** (Scheme 4). The "clickable" quinoxazolinone **6** obtained in

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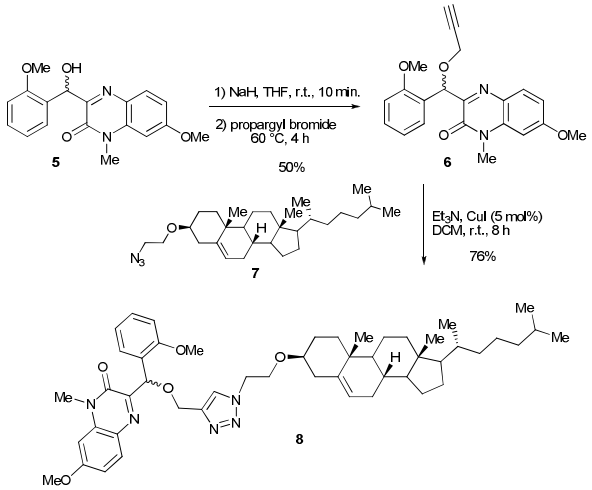
50% yield in the presence of NaH and propargyl bromide was next reacted with cholesterol azide **7** in the presence of CuI and triethylamine in DCM at room temperature. The desired quinoxalinone cholesterol conjugate **8** was formed in convenient 76% yield, and displayed fluorescence properties in line with whose of **5** (quantum yield of 0.08 upon an excitation at 366 nm in THF at 25 °C).




**Scheme 4** Application to the preparation of the fluorescently labelled cholesterol derivative **8**.

## Conclusions

In summary, a novel access to benzoylquinoxalin-2(1H)-ones through an unprecedented metal-free oxidative ring contraction of 1,5-benzodiazepin-2-ones is reported. Of significance, this reaction was found to be operationally simple, not sensitive to moisture or oxygen and applicable to electron-rich/electron-deficient phenyl rings. A fluorescent and bioconjugatable quinoxalinone was next prepared and used for the construction of a cholesterol probe displaying suitable optical properties. Finally, this study brings to light the yet unprecedented fluorogenic properties of benzoylquinoxalin-2(1H)-ones that could be leveraged into biological applications.

## Experimental

Commercially available reagents were used without further purification. Column chromatography purifications were performed on silica gel (40-63 µm). Thin-layer chromatography (TLC) analyses were carried out on F-254 aluminum sheets. The spots were visualized through illumination with UV lamp (λ = 254 or 365 nm) and/or staining with $KMnO_4$. Phosphate buffered saline PBS (0.1 M, pH 7.4) was prepared using water purified with a Milli-Q system (purified to 18.2 MΩ.cm).

**Instruments and methods**

IR spectra were recorded with a universal ATR sampling accessory. $^1H$ and $^{13}C$ NMR spectra (C13APT or C13CPD experiments) were recorded on a 300 MHz spectrometer. Chemical shifts are expressed in parts per million (ppm) from the residual non-deuterated solvent signal: $CDCl_3$(δH = 7.26, δC = 77.16), DMSO-d6 (δH = 2.50, δC = 39.52). High-resolution mass spectra (HRMS) were obtained using an orthogonal acceleration time-of-flight (oa-TOF) mass spectrometer equipped with an electrospray source and in the positive and negative modes (ESI+/-). UV-visible spectra were obtained using either a rectangular quartz cell (Open Top, 10 × 10 mm, 3.5 mL). Fluorescence spectroscopic studies in solution were performed with a semi-micro quartz fluorescence cell (Hellma, 104F-QS, light patch base thickness 10 × 4 mm, chamber volume: 1400 µL for the determination of quantum yields, and chamber volume: 3.5 mL for all others studies), with excitation and emission slit widths of 5 nm. Solvents for spectroscopy were spectroscopic grade. Fluorescence quantum yields in 0.1 M PBS pH 7.4 were measured at 25 °C by a relative method using anthracene (ΦF = 0.27 in ethanol λex 366 nm) as a standard. The following equation was used to determine the relative fluorescence quantum yield in solution:

$$\Phi F(x) = (A_S/A_X)(F_X/F_S)(n_X/n_S)^2 \Phi F(s)$$

where A is the absorbance (in the range of 0.01-0.1 A.U.), F is the area under the emission curve, n is the refractive index of the solvents (at 25 °C) used in measurements, and the subscripts s and x represent standard and unknown, respectively. The following refractive index values were used: 1.333 for aq. $H_2SO_4$, 1.407 for THF, and 1.337 for PBS.

**Synthesis**

**Procedures for the synthesis of 1,5-benzodiazepin-2-ones 1a-l and 4.**

Compounds **1a**,[28] **1b**,[29] **1d**,[28] **1f**,[30] **1g**,[31] **1h**,[32] **1l**[33] were prepared according to known procedures.

**4-(2-Methoxyphenyl)-1-methyl-1,5-benzodiazepin-2-one 1c**. To a solution of 4-(2-hydroxyphenyl)-1-methyl-1,5-benzodiazepin-2-one[27] (266 mg, 1 mmol, 1 equiv.) in anhydrous DMF (5 mL), was added $K_2CO_3$ (414 mg, 3 mmol, 3 equiv.). The mixture was stirred for 10 to 15 min before the addition of methyl iodide (494 µL, 8 mmol, 8 equiv.). The reaction mixture was maintained at room temperature overnight. After completion the mixture was diluted with 40 mL of AcOEt, and the organic layers was washed with water (3 × 30 mL). The organic phase was finally dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (Cyclohexane/ EtOAc from 80:20 to 70:30) to obtain the desired product (198 mg, 71 % yield) as a white solid, mp = 118- 120 °C. IR (ATR): vmax: 1661 (CN), 1595 (CO). $^1H$ NMR (300 MHz, $CDCl_3$): δ = 3.04 (d, *J* = 12.0 Hz, 1H), 3.38 (s, 3H), 3.87 (s, 3H), 4.12 (d, *J* = 12.0 Hz, 1H), 6.92-6.99 (m, 2H), 7.20-

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7.29 (m, 3H), 7.35-7.44 (m, 2H), 7.51-7.54 (dd, *J* = 9.0 and 3.0 Hz, 1H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 36.3, 42.9, 55.5, 111.3, 120.9, 121.6, 125, 126.3, 127.7, 128.7, 130.6, 131.9, 135.1, 141.3, 158.2, 164.1, 167.7 ppm. HRMS (ESI+): calcd. for $C_{17}H_{17}N_2O_2$ $[M+H]^+$ 281.1234; found 281.1226.

**2-(1-methyl-2-oxo-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)phenyl acetate 1e**. To a solution of 4-(2-hydroxyphenyl)-1-methyl-1,5-benzodiazepin-2-one [28] (1 mmol) in anhydrous THF (10 mL) at 0 °C, was added NaH (60% in mineral oil, 0.044 g, 1.1 mmol, 1.1 equiv.). The mixture was stirred for 10 to 15 min before the addition of acetyl chloride (0.106 mL, 1.5 mmol, 1.5 equiv.). The reaction mixture was maintained at room temperature for 2 h, before removing the solvent under reduced pressure. The crude material was purified by flash column chromatography on silica gel (Cyclohexane/ EtOAc from 100:0 to 85:15) to obtain the desired product (200 mg, 91 % yield) as a white solid, mp = 168- 170 °C. IR (ATR): vmax: 1661 (CN), 1595 (CO), 1610 (CO). $^1$H NMR (300 MHz, $CDCl_3$): δ = 2.83 (s, 3H), 3.10 (sb, 1H), 3.44 (s, 3H), 3.96 (sb, 1H), 7.16-7.19 (m, 1H), 7.29-7.43 (m, 6H), 7.92 (d, J = 6.0 Hz, 1H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 20.4, 34.4, 41.4, 120.9, 122.7, 124.3, 125.3, 125.7, 126.5, 129.2, 130.4, 130.9, 134.3, 140.3, 147.9, 159.2, 165.9, 168.5 ppm. HRMS (ESI+): calcd. for $C_{18}H_{17}N_2O_3$ $[M+H]^+$ 309.1234; found 309.1239.

**8-Methoxy-4-(2-methoxyphenyl)-1-methyl-1,5-benzodiazepin-2-one 1i**. To a solution of 4-(2-hydroxyphenyl)-8-methoxy-1-methyl-1,5-benzodiazepin-2-one[34] (162 mg, 0.55 mmol, 1 equiv.) in anhydrous DMF (3 mL), was added $K_2CO_3$ (215 mg, 1.68 mmol, 3 equiv.). The mixture was stirred for 10 to 15 min before the addition of methyl iodide (272 µL, 4.4 mmol, 8 equiv.). The reaction mixture was maintained at room temperature overnight. After completion the mixture was diluted with 40 mL of AcOEt, and the organic layers was washed with water (3 × 30 mL). The organic phase was finally dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (Cyclohexane/ EtOAc from 80:20 to 70:30) to obtain the desired product (111.5 mg, 65 % yield) as a yellow solid, mp = 68- 70 °C. IR (ATR): vmax: 1663 (CN), 1597 (CO). $^1$H NMR (300 MHz, DMSO-d6): δ = 3.07 (d, J = 12.0 Hz, 1H), 3.26 (s, 3H), 3.79 (s, 3H), 3.87 (s, 3H), 3.91 (d, J = 12.0 Hz, 1H), 6.86-7.03 (m, 3H), 7.16 (d, J = 9.0 Hz, 1H), 7.38-7.52 (m, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-d6): δ = 34.6, 42.7, 55.4, 55.5, 109.6, 111.9, 113.6, 120.3, 123.1, 128, 128.1, 130.2, 131.9, 141.6, 155.8, 157.7, 163.1, 166.0 ppm. HRMS (ESI+): calcd. for $C_{18}H_{19}N_2O_3$ $[M+H]^+$ 311.1396; found 311.1390.

**1-Methyl-7-nitro-4-phenyl-1,5-benzodiazepin-2-one 1j and 1-methyl-8-nitro-4-phenyl-1,5-benzodiazepin-2-one 1k**. To a solution of containing a mixture of 7- and 8-nitro-4-phenyl-1,5-benzodiazepin-2-one[35] (500 mg, 1.77 mmol) in anhydrous THF (18 mL) at 0 ° C, was added NaH (95% in mineral oil, 0.047 g, 1.96 mmol, 1.1 equiv.). The mixture was stirred for 10 to 15 min before the addition of methyl iodide (0.220 mL, 3.56 mmol, 2 equiv.). The reaction mixture was maintained overnight at room temperature, before removing the solvent under reduced pressure. The crude material was purified by flash column chromatography on silica gel (Cyclohexane/EtOAc from 90:10, 80:20 to 50/50), allowing the separation of the two regioisomers **1j** and **1k**. It should be stressed that the position of the nitro substituent on the aromatic ring was assigned retrospectively from the NOESY experiment carried out with quinoxalinone **2j** (c.f. Supporting Information).

**1-Methyl-7-nitro-4-phenyl-1,5-benzodiazepin-2-one 1j** (126 mg, 24 % yield) was obtained as yellow solid, mp = 198-200 °C. IR (ATR): vmax: 1671 (CN), 1615 (CO). $^1$H NMR (300 MHz, $CDCl_3$): δ = 2.98 (d, *J* = 12.0 Hz, 1H), 3.46 (s, 3H), 4.26 (d, *J* = 12.0 Hz, 1H), 7.43-7.59 (m, 4H), 8.09-8.17 (m, 3H), 8.24 (d, *J*= 3.0 Hz, 1H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 35.4, 40.1, 117.9, 120, 128.2, 128.2, 129, 132.2, 135.3, 136.5, 145.1, 146.2, 163.3, 165.8 ppm. HRMS (ESI+): calcd. for $C_{16}H_{14}N_3O_3$ $[M+H]^+$ 296.1022; found 296.1018.

**1-Methyl-8-nitro-4-phenyl-1,5-benzodiazepin-2-one 1k**. (227 mg, 43 % yield) was obtained as yellow solid, mp = 188-190 °C. IR (ATR): vmax: 1671 (CN), 1576 (CO). $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.03 (d, *J* = 12.0 Hz, 1H), 3.50 (s, 3H), 4.32 (d, *J* = 12.0 Hz, 1H), 7.49-7.63 (m, 4H), 8.15-8.22 (m, 3H), 8.40 (d, *J* = 3.0 Hz, 1H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 35.6, 39.9, 120.7, 122.5, 123.4, 128, 129, 132, 136.6, 140.2, 141.6, 144.4, 162.7, 165.8 ppm. HRMS (ESI+): calcd. for $C_{16}H_{14}N_3O_3$ $[M+H]^+$ 296.1022; found 296.1020.

**3-Bromo-4-phenyl-1,5-benzodiazepin-2-one 4**.[36] To a solution of 4-phenyl-1,5-benzodiazepin-2-one (500 mg, 2.11 mmol, 1 equiv.) in DMSO (6.3 mL), was added NBS (381 mg, 2.11 mmol, 1 equiv.). The mixture was stirred for 5 h at room temperature. The solution was diluted with DCM, and successively washed with a solution of saturated aq. $NaHCO_3$ and $Na_2S_2O_3$, then with brine. The combined phase was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (Cyclohexane/EtOAc 90:10) to obtain the 3-bromo-4-phenyl-1,5-benzodiazepin-2-one **4** (578 mg, 1.8 mmol, 87 %) as a pale yellow solid, mp = 175-177 °C. IR (neat): 3162, 3065, 1675, 1644, 1573, 1480, 1327, 1239. $^1$H NMR (300 MHz, DMSO-d6): δ 11.21 (s, 1H), 8.04 (d, *J* = 6.6 Hz, 2H), 7.68-7.44 (m, 4H), 7.44-7.19 (m, 3H), 6.06 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-d6): δ 162.7, 155.4, 139.1, 136.3, 131.3, 129.1, 128.8, 128.1, 127.6, 127.5, 124.5, 120.5 ppm. HRMS (ESI+): calcd. for $C_{15}H_{12}N_3O^{79}Br$ $[M+H]^+$ 315.0133; found 315.0123 and calcd. for $C_{15}H_{12}N_3O^{81}Br$ $[M+H]^+$ 317.0113; found 317.0108.

**General Procedure for the Synthesis of Quinoxalin-2-ones 2a-l**

To a solution of 1,5-benzodiazepin-2-one 1a-l (0.5 mmol) in DMSO (1.5 mL) in a flask equipped with a rubber septum (with a needle inserted for preventing overpressure), was added N-bromosuccinimide (36 mg, 0.2 mmol, 0.4 eq.) at room temperature. Unless stated, the mixture was then heated to 110 °C, and stirred for 6 h if not specified. Thereafter, to the solution cooled to room temperature were successively added dichloromethane (10 mL), a solution of saturated aq. $NaHCO_3$ (4 mL), and a solution of saturated aq. $Na_2S_2O_3$ (4 mL). The resulting organic layer was separated, and the aqueous layer

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was extracted with dichloromethane (3 × 10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (Cyclohexane/EtOAc from 100:0 to 50:50) to obtain the desired product.

**3-Benzoylquinoxalin-2(1H)-one 2a** [37] (65 mg, 0.26 mmol, 52 %), was obtained as a yellow solid, mp = 258-260 °C. $^1$H NMR (300 MHz, DMSO-d6): δ = 7.35-7.43 (m, 2H), 7.55-7.60 (m, 2H), 7.63-7.68 (m, 1H), 7.71-7.77 (m, 1H), 7.82-7.85 (dd, *J*= 9.0 and 3.0 Hz, 1H), 7.96-7.99 (m, 2H), 12.87 (s, 1H) ppm. $^{13}$C NMR (75 MHz, DMSO-d6): δ = 115.9, 123.8, 129, 129.1, 129.7, 131.2, 131.7, 132.7, 134.6, 134.8, 153.4, 158.3, 192.4 ppm.

**3-Benzoyl-1-methylquinoxalin-2(1H)-one 2b.**[38] The reaction was stirred at 110 °C for 12 h. **2b** (74 mg, 0.28 mmol, 55 %) was obtained as a yellow solid, mp = 155-157 °C. IR (ATR): vmax: 1670 (CO), 1650 (CN), 1590 (CO). $^1$H NMR (300 MHz, DMSO-d6): δ = 3.68 (s, 3H), 7.46 (t, *J* = 6.0 Hz, 1H), 7.55-7.60 (m, 2H), 7.68-7.77 (m, 3H), 7.89 (d, *J* = 6.0 Hz, 1H), 7.98 (d, *J* = 6.0 Hz, 2H), ppm. $^{13}$C NMR (75 MHz, DMSO-d6): δ = 29, 115.2, 123.9, 129, 129.7, 129.9, 131.7, 132, 133.9, 134.4, 134.6, 152.8, 154.8, 192.2 ppm. HRMS (ESI+): calcd. for $C_{16}H_{13}N_2O_2$ $[M+H]^+$ 265.0977 ; found 265.0977.

**3-(2-Methoxybenzoyl)-1-methylquinoxalin-2(1H)-one 2c**. [39] The reaction was stirred at 110 °C for 12 h. **2c** (96 mg, 0.33 mmol, 65 %), was obtained as a white solid, mp = 173-175 °C. IR (ATR): vmax: 1659 (CO), 1645 (CN), 1590 (CO). $^1$H NMR (300 MHz, DMSO-d6): δ = 3.51 (s, 3H), 3.69 (s, 3H), 7.14-7.19 (m, 2H), 7.42 (t, *J* = 6.0 Hz, 1H), 7.65-7.73 (m, 3H), 7.81-7.94 (m, 2H), ppm. $^{13}$C NMR (75 MHz, DMSO-d6): δ = 28.8, 56.3, 113.3, 115.1, 121.2, 123.8, 124.4, 129.5, 129.9, 131.3, 131.6, 133.4, 136.3, 152.7, 157.1, 160, 190.7 ppm. HRMS (ESI+): calcd. for $C_{17}H_{15}N_2O_3$ $[M+H]^+$ 295.1083; found 295.1082.

**2-(4-Methyl-3-oxo-3,4-dihydroquinoxaline-2-carbonyl)phenyl acetate 2e**. The reaction was stirred at 130 °C for 12 h. **2e** (72 mg, 0.22 mmol, 45 %), was obtained as a white solid, mp = 148-150 °C. IR (ATR): vmax: 1660 (CO), 1626 (CN), 1604 (CO). $^1$H NMR (300 MHz, DMSO-d6): δ = 1.84 (s, 3H), 3.69 (s, 3H), 7.28-7.31 (dd, *J* = 6.0 and *J*= 3.0 Hz, 1H), 7.44-7.49 (m, 2H), 7.68-7.80 (m, 3H), 7.85-7.88 (dd, *J* = 6.0 and 3.0 Hz, 1H), 7.95-7.98 (dd, *J* = 6.0 and 3.0 Hz, 1H) ppm. $^{13}$C NMR (75 MHz, DMSO-d6): δ = 20.2, 28.9, 115.2, 124.2, 124.3, 126.5, 128, 129.9, 131.3, 131.6, 132.2, 133.7, 135.3, 150, 152.6, 155, 168.3, 190.3 ppm. HRMS (ESI+): calcd. for $C_{18}H_{15}N_2O_4$ $[M+H]^+$ 323.1032; found 323.1032.

**3-(4-nitrobenzoyl)quinoxalin-2(1H)-one 2f** [40] (90 mg, 0.30 mmol, 61%), was obtained as a yellow solid, 292 °C (decomposition). IR (ATR): vmax: 2834, 1698, 1652, 1604, 1510, 1349. $^1$H NMR (300 MHz, DMSO-d6): δ = 7.36-7.43 (m, 2H), 7.68 (t, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 8.25 (d, *J* = 9.0 Hz, 2H), 8.36 (d, *J* = 9.0 Hz, 2H), 12.95 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-d6): δ = 115.9, 123.8, 123.9, 129.2, 131.0, 131.2, 132.2, 132.9, 139.1, 150.5, 153.3, 154.7, 191.2. HRMS (ESI+): calcd. for $C_{15}H_{10}N_3O_4$ $[M+H]^+$ 296.0671 ; found 296.0668.

**Mixture of 3-Benzoyl-6-methylquinoxalin-2(1H)-one and 3-benzoyl-7-methylquinoxalin-2(1H)-one 2g** (93 mg, 0.35 mmol, 67 %), was obtained as a yellow solid as an inseparable mixture of regioisomers in a 0.54:1 ratio. IR (ATR): vmax: 2843 (NH), 1694 (CO), 1650 (CN), 1616 (CO). $^1$H NMR (300 MHz, DMSO-d6): δ = 2.39 (s, 3H), 2.45 (s, 1.64H), 7.18-7.32 (m, 2.85H), 7.47-7.64 (m, 5.6H), 7.70-7.76 (m, 2.3H), 7.94-7.97 (m, 2.23H), 12.81 (s, 1.64H) ppm. $^{13}$C NMR (75 MHz, DMSO-d6): δ = 20.8, 21.9, 115.9, 116.1, 125.7, 129.1, 129.3, 129.5, 130, 130.1, 130.9, 131.6, 133.1, 133.5, 133.7, 135, 135.1, 135.2, 142.8, 153.8, 154, 193.0 ppm. HRMS (ESI+): calcd. for $C_{16}H_{13}N_2O_2$ $[M+H]^+$ 265.0977 ; found 265.0967.

**3-Benzoyl-7-methoxyquinoxalin-2(1H)-one 2h** (82 mg, 0.29 mmol, 59%), was obtained as a yellow solid, mp = 206-208 °C. IR (ATR): vmax: 1683, 1651, 1495, 1372, 1289. $^1$H NMR (300 MHz, DMSO-d6): δ = 12.79 (s, 1H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 2H), 7.36-7.29 (m, 3H), 3.81 (s, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-d6): δ = 55.6, 110.2, 116.7, 121.2, 126.8, 128.9, 129.5, 131.8, 134.4, 134.5, 152.9, 155.6, 156.3, 192.4 ppm. HRMS (ESI-): calcd. for $C_{16}H_{11}N_2O_3$ [M-H]- 279.0770; found 279.0769.

**7-Methoxy-3-(2-methoxybenzoyl)-1-methylquinoxalin-2(1H)-one 2i** (66 mg, 0.20 mmol, 40%), was obtained as a yellow solid, mp = 178-180 °C. IR (ATR): vmax: 1766 (CO), 1643 (CN), 1519 (CO). 1H NMR (300 MHz, DMSO-d6): δ = 3.45 (s, 3H), 3.60 (s, 3H), 3.77 (s, 3H), 7.07-7.12 (m, 2H), 7.25-7.30 (m, 2H), 7.52-7.64 (m, 2H), 7.83-7.86 (dd, *J* = 6.0 and 3.0 Hz, 1H) ppm. $^{13}$C NMR (75 MHz, DMSO-d6): δ = 29.5, 55.6, 56.3, 111.4, 113.2, 116, 119.9, 121.2, 124.5, 127.6, 129.9, 132.5, 136.2, 152.3, 155.6, 157.5, 160, 190.8 ppm. HRMS (ESI+): calcd. for $C_{18}H_{17}N_2O_4$ $[M+H]^+$ 325.1188; found 325.1196.

**3-Benzoyl-1-methyl-6-nitroquinoxalin-2(1H)-one 2j** (128 mg, 0.41 mmol, 82 %) was obtained as a yellow solid, was obtained as a yellow solid, mp = 268-270 °C. IR (ATR): vmax: 1702 (CO), 1678 (CN), 1658 (CO). $^1$H NMR (300 MHz, DMSO-d6): δ = 3.71 (s, 3H), 7.56-7.61 (m, 2H), 7.74-7.79 (m, 1H), 7.89 (d, *J* = 3Hz, 1H), 8.01-8.05 (m, 2H), 8.51-8.61 (m, 2H) ppm. $^{13}$C NMR (75 MHz, DMSO-d6): δ = 29.6, 116.6, 125, 125.9, 129, 129.8, 130.8, 134, 134.9, 138.9, 142.8, 152.9, 157,0, 191.4 ppm. HRMS (ESI+): calcd. for $C_{16}H_{12}N_3O_4$ $[M+H]^+$ 310.0828; found 310.0822.

**3-Benzoyl-1-methyl-7-nitroquinoxalin-2(1H)-one 2k** (115 mg, 0.37 mmol, 74 %), was obtained as a yellow solid, was obtained as a yellow solid, mp = 193-195 °C. IR (ATR): vmax: 1679 (CO), 1649 (CN), 1594 (CO). $^1$H NMR (300 MHz, DMSO-d6): δ = 3.75 (s, 3H), 7.56-7.61 (m, 2H), 7.74-7.79 (m, 1H), 8.01-8.24 (m, 4H), 8.42 (d, *J* = 3.0 Hz, 1H) ppm. $^{13}$C NMR (75 MHz, DMSO-d6): δ = 29.4, 110.8, 118, 129, 129.8, 131.2, 133.9, 134.6, 135, 135.1, 148.4, 152.7, 158.2, 191.6 ppm. HRMS (ESI+): calcd. for $C_{16}H_{12}N_3O_4$ [M+H]+ 310.0828; found 310.0829.

**Procedures for the synthesis of the quinoxalinone-cholesterol conjugate 8**

**3-(Hydroxy(2-methoxyphenyl)methyl)-7-methoxy-1-methylquinoxalin-2(1H)-one 5**. To a solution of **2i** (33 mg, 0.1 mmol) in MeOH (5 ml) was added $NaBH_4$ (4.5 mg, 0.12 mmol, 1.2 eq.). The mixture was stirred at room temperature for 10 min, before removing the solvent under reduced pressure.

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Thereafter, the crude mixture was washed with $Et_2O$ to obtain the desired product (32 mg, 0.098 mmol, 98 %) as a yellow solid, mp = 223-225 °C. IR (ATR): vmax: 3415( H), 1653(CN), 1597 (CO). $^1$H NMR (300 MHz, DMSO-d6): δ = 3.61 (s, 3H), 3.67 (s, 3H), 3.81 (s, 3H), 5.66 (s, 1H), 6.39 (s, 1H), 6.89-6.95 (m, 2H), 7.25-7.32 (m, 3H), 7.37 (d, *J* = 6.0 Hz, 1H), 7.48 (d, *J* = 6.0 Hz, 1H) ppm. $^{13}$C NMR (75 MHz, DMSO-d6): δ = 29, 55.5, 55.6, 65.2, 110.8, 111, 115.7, 118.9, 120, 127.4, 127.5, 128.2, 130.3, 132.3, 152.9, 155.4, 156.2, 160.6 ppm. HRMS (ESI+): calcd. for $C_{18}H_{19}N_2O_4$ [M+H]+ 327.1345; found 327.1344.

**7-Methoxy-3-((2-methoxyphenyl)(prop-2-yn-1-yloxy)methyl)-1-methylquinoxalin-2(1H)-one 6**. To a solution of **5** (32 mg, 0.1 mmol) in DMF (2 ml) was added NaH (3 mg, 1.2 eq.) at room temperature. After stirring the mixture for 10 min, the propargyl bromide (9 µl, 0.12 mmol, 1.2 eq.) was added and the reaction was heated at 60 °C for 6 h. Thereafter, the crude mixture was extracted with water/dichloromethane, before removing the solvent under reduced pressure. The crude material was purified by flash column chromatography on silica gel (Cyclohexane/EtOAc from 100:0 to 50:50) to obtain the desired product **6** (19 mg, 0.5 mmol, 50 %) as a yellow solid, mp = 171-173 °C. $^1$H NMR (300 MHz, DMSO-d6): δ = 3.41 (s, 1H), 3.60 (s, 3H), 3.75 (s, 3H), 3.83 (s, 3H), 4.27 (s, 2H), 6.45 (s, 1H), 6.93-7.02 (m, 2H), 7.25-7.30 (m, 4H), 8.49 (d, J= 6.0 Hz, 1H) ppm. $^{13}$C NMR (75 MHz, DMSO-d6): δ = 29.0, 55.6, 56.9, 71.7, 77.2, 80.3, 111.1, 115.7, 119.5, 120.1, 126.5, 127.3, 127.8, 129.1, 132.4, 153, 155.4, 156.8, 157.7 ppm. HRMS (ESI+): calcd. for $C_{21}H_{21}N_2O_4$ $[M+H]^+$ 365.1501; found 365.1512.

**3-(((1-(2-cholesterolethyl)-1H-1,2,3-triazol-4-yl)methoxy)(2-methoxyphenyl)methyl)-7-methoxy-1-methylquinoxalin-2(1H)-one 8**. To a mixture of compound **6** (18 mg, 0.05 mmol) and cholesterol azide **7**[41] (35 mg, 0.075 mmol, 1.5 eq.) in DCM (5 mL) was added CuI (2 mg, 0.005 mmol, 0.1 eq.) and $Et_3N$ (10 µl, 0.075 mmol, 1.5 eq.). The reaction mixture was stirred at room temperature for 3 h. The crude reaction was filtered through Celite®, and the filtrate concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (Cyclohexane/EtOAc from 100:0 to 50:50) to obtain the desired product **8** (31 mg, 0.038 mmol, 76% yield) as a yellow solid, mp = 160-162 °C. $^1$H NMR (300 MHz, DMSO-d6): δ = 0.84-1.49 (m, 30H), 1.74-2.24 (m, 11H), 3.61 (s, 3H), 3.71 (s, 3H), 3.78 (s, 2H), 3.81 (s, 3H),4.46 (s, 2H), 4.59-4.68 (m, 2H), 6.42 (s, 1H), 6.94-7.01 (m, 2H), 7.23-7.39 (m, 4H), 7.48 (d, *J* = 6.0Hz, 1H), 8.06 (s, 1H) ppm. $^{13}$C NMR (75 MHz, DMSO-d6): δ = 18.5, 18.9, 20.5, 22.3, 22.6, 23.2, 23.8, 27.4, 27.7, 27.8, 29, 31.3, 31.3, 35.1, 35.6, 36.1, 45.7, 49.5, 49.7, 55.5, 55.6, 56.1, 63.1, 65.6, 65.7, 72.3, 78.3, 78.4, 111, 111.2, 115.7, 119.4, 120.1, 121.1, 123.7, 124.4, 126.9, 127.3, 127.7, 128.8, 132.4, 140.2, 143.7, 153.1, 155.4, 156.7, 158.1 ppm. HRMS (ESI+): calcd. for $C_{50}H_{70}N_5O_5$ $[M+H]^+$ 820.5394; found 820.5393.

#### Fluorescence turn on of quinoxalinone 2i

To a 20 µM solution of the quinoxalinone **2i** in 3 mL of PBS buffer (0.1 M pH 7.4) in semi-micro quartz fluorescence cell (Hellma, 104F-QS, 10 × 4 mm, Chamber volume 3.5 mL) was added $NaBH_4$ (2.34 mg, 10 eq.). Emission spectra (upon an excitation at 366 nm in PBS 7.4 at 25 °C) were recorded before and after the addition of $NaBH_4$.

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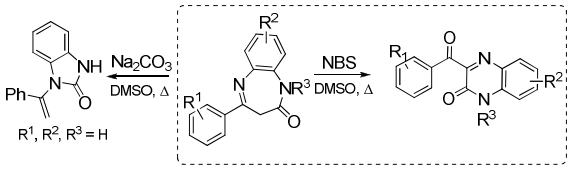


Herein is reported a practical method for the construction of 3-benzoylquinoxalinones from benzodiazepinones in the presence of DMSO which serves both as solvent and oxidant.