Synthesis and Reactivity of 2,3-Dihydro-1*H*-2,3-benzodiazepine-1,4(5*H*)-dione

Frédéric J.-J. Bihel,* Malik Hellal, Jean-Jacques Bourguignon

Institut Gilbert Laustriat, UMR 7175 CNRS, Département Pharmacochimie de la Communication Cellulaire, Faculté de pharmacie, Université Strasbourg I, 74 route du rhin, BP60024, 67400 Illkirch Graffenstaden, France
Fax +33(3)90244310; E-mail: frederic.bihel@pharma.u-strasbg.fr

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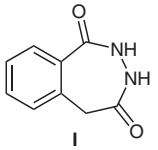
Abstract: Based on an orthogonal protective group strategy dealing with N-protected hydrazine, we established for the first time a highly efficient synthetic pathway leading to 2,3-benzodiazepine-1,4-dione. Moreover, the versatile reactivities exhibited by this 2,3-benzodiazepine-1,4-dione were evaluated towards both benzylation and amination reactions.

Key words: benzodiazepine, hydrazine, amides, aminations, bicyclic compounds

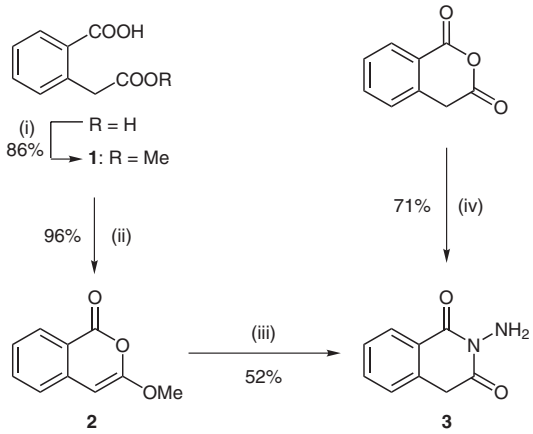
During the course of our investigations dealing with pyridazine-3,6-dione and phthalazine-1,4-dione scaffolds, extensive work has been done focusing on the regio- and chemoselective functionalization of the amide functions to provide either amidines through nucleophilic substitution or iminoaryl groups through palladium-catalyzed reactions.[1] Most of the synthesized compounds, derived from the six-membered azine ring, were found pharmacologically active on various targets (receptors or enzymes) involved in pathologies such as Alzheimer's disease or pain.[2] In our quest of new bioactive compounds, we focused our research on design, synthesis, and functionalization of the 2,3-benzodiazepine (2,3-BZD) scaffold, as a seven-membered-ring homologue of the 2,3-phthalazine scaffold, and consequently report here a new convenient route to the 2,3-BZD-1,4-dione (**I**) (Figure 1). Moreover, the reactivity of this new scaffold toward both amination and benzylation reactions was examined.



I

Figure 1 2,3-Dihydro-1*H*-benzodiazepine-1,4(5*H*)-dione (**I**)

A unique example of the 2,3-BZD-1,4-dione (**I**) synthesis was reported in 1944, when Whitmore and Cooney claimed that the reaction of homophthalic anhydride with hydrazine hydrate in boiling ethanol led to the 2,3-BZD-1,4-dione (**I**).[3] However, this result was later disproved by several reports in which, using the same experimental conditions, only the *N*-aminoisoquinoline-1,3-dione (**3**) was isolated.[4] We also tried to reproduce the procedure reported by Whitmore and Cooney, but only the compound **3** was obtained in 71% yield (Scheme 1). The most electrophilic carbonyl carbon at the 3-position of the 1*H*-isochromene-1,3(4*H*)-dione undergoes a first nucleophilic attack by hydrazine affording a hydrazide intermediate, which exhibits both amine and amide functions as possible nucleophilic groups for cyclocondensation. Surprisingly, the observed cyclization involved the amide nitrogen, which is less nucleophilic than the amino group, leading to the 6- membered ring **3**.[4] As an alternative pathway, we synthesized the 3-methoxyisocoumarine **2**, in which the only electrophilic carbonyl carbon is at the position 1. However, the reaction with hydrazine led again to the six-membered ring **3**, as previously observed (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) MeOH, H_2SO_4, Δ; (ii) TFAA, CH_2Cl_2, 0 °C; (iii) $NH_2NH_2{\cdot}H_2O$, MeOH, r.t.; (iv) $NH_2NH_2{\cdot}H_2O$, EtOH, Δ.

It appeared that the amine function did not trigger the expected seven-membered-ring cyclization, which may be explained by the *syn*-position of the amine function toward the oxygen atom of the amide function. Consequently, it seemed critical to use a substituted hydrazine in order to modify the spatial position of the amine group toward the amide function. In agreement with this hypothesis, the synthesis of 2,3-dimethyl-2,3-BZD-1,4-dione was reported by Rosen et al., who used the 1,2-dimethylhydrazine to perform the cyclization.[4] However, the main limitation of this procedure was the impossibility to remove the alkyl groups of the resulting 2,3-dimethyl-2,3-BZD-1,4-dione. So, we chose to develop an orthogonal protective group strategy in which the first amine function of hy-

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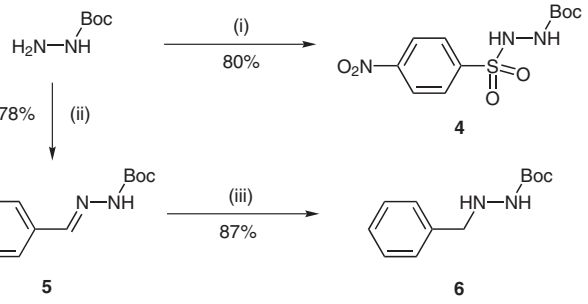
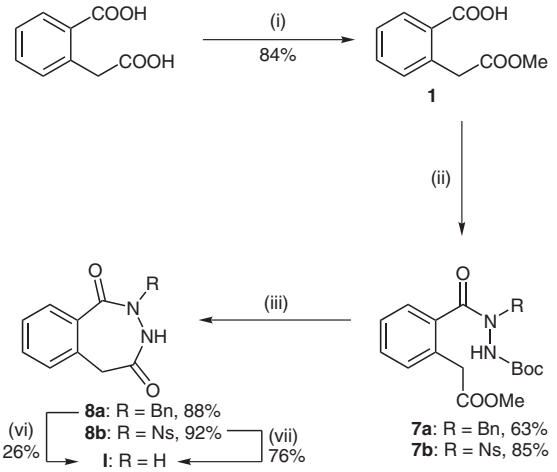
drazine was protected by a Boc group, whereas the second amine function was protected either by a nosyl moiety (**4**) or by a benzyl group (**6**) (Scheme 2).[5] Both benzyl and nosyl protections afford a satisfactory nucleophilic character of the protected amine allowing the coupling reaction with the carboxylic acid derivative **1**,[6] to obtain the compounds **7a** and **7b** in 63 and 85% yield, respectively (Scheme 3). A trifluoroacetic acid treatment led to the cleavage of the Boc group which was followed by a spontaneous cyclization step to provide the 2,3-BZD-1,4-diones **8a** and **8b** in 88% and 92% yield, respectively. The cleavage of the benzyl moiety was performed by hydrogenolysis using palladium chloride as catalyst.[7] However, the deprotection remained incomplete after a reaction time of 24 hours and the expected 2,3-BZD-1,4-dione (**I**) was obtained in a poor 26% yield. On the contrary, the cleavage of the nosyl moiety was easily performed in mild conditions by treatment of **8b** with thiophenol under basic conditions,[8] leading to the unsubstituted 2,3-BZD-1,4-dione (**I**) in 76% yield.



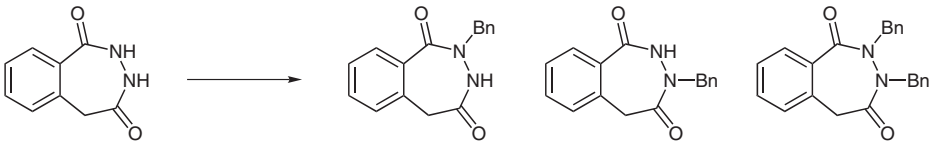
Scheme 2 *Reagents and conditions*: (i) NsCl, K_2CO_3, r.t., 1 h; (ii) PhCHO, THF, r.t., 1 h; (iii) H_2 (60 psi), Pd/C, MeOH, 2 h.

We next focused our study on the reactivity of this 2,3-BZD-1,4-dione (**I**) towards the benzylation of the amide function and its conversion into an amidine. A standard benzylation using benzyl bromide was performed in the presence of NaH in DMF, leading to a mixture of three compounds: monobenzylated derivatives (2-benzyl **8a** and 3-benzyl **9**) were both isolated in 22% yield, whereas the 2,3-dibenzylated compound **10** was isolated in 56% yield (Table 1). The same results were obtained with K_2CO_3 in DMF. However, no benzylation was detected under Mitsunobu conditions. Considering the fact that **8a** and **9** were obtained in the same yield, we can assume that both amide groups of 2,3-BZD-1,4-dione (**I**) exhibit an equal nucleophilicity toward this benzylation reaction, despite the difference between benzamide and phenylacetamide moieties. Moreover, the dibenzylated compound **10** was obtained in the highest yield (56%), highlighting the fact that as soon as one of the amide functions was benzylated, the nucleophilicity of the second one was increased. Consequently, it appears very difficult to regioselectively alkylate a single amide group of compound **I**. Among the alternatives, an initial alkylation of Boc-hydrazine would lead to the corresponding 2-alkyl-2,3-BZD-1,4-dione, while the alkylation of the compound **8b**, followed by nosyl deprotection, would provide the corresponding 3-alkyl-2,3-BZD-1,4-dione.



Scheme 3 *Reagents and conditions*: (i) MeOH, H_2SO_4 (cat.), Δ; (ii) **4** or **6**, HBTU, DIPEA, DMF, r.t., 12 h; (iii) TFA, CH_2Cl_2, 1 h, r.t.; (iv) H_2 (60 psi), $PdCl_2$, AcOH, EtOAc, r.t., 12 h; (v) PhSH, Cs_2CO_3, DMF, r.t., 3 h.

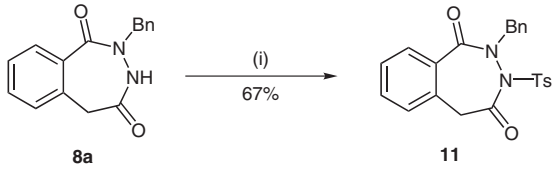
Table 1 Benzylation of the 2,3-Benzodiazepine-1,4-dione (**I**)



Benzylating reagent	Equiv	Conditions	T (°C)	Time (h)	Products		
					8a	**9**	**10**
BnBr	1	NaH, DMF	0	1	22	22	56
BnBr	2	NaH, DMF	0	1	–[a]	–[a]	89
BnBr	1	K_2CO_3, DMF	r.t.	24	24	20	53
BnOH	1	DIAD, Ph_3P, DMF	r.t.	24	–[a]	–[a]	–[a]

[a] Not detected.

The cyclic amidine represents an important functional group in medicinal chemistry and can be found in many FDA-approved drugs (i.e., clozapine). The most common and convergent strategies for amidine synthesis are based on substitution by an amine of an activated amide intermediate such as imidoyl chloride or O-triflated imidate.[9] Unfortunately, our initial attempts to activate the amide functions of 2,3-BZD-1,4-dione (**I**) failed. Indeed, along with the fact there is a putative competition between both amides, the main problem was the lack of solubility of the compound **I**, especially in solvents such as THF, MeCN, or pyridine which are commonly used in this field. Several attempts under acidic conditions ($POCl_3$) failed, most of them led to degradation. Even the milder procedure using *N*,*N*-dimethyl-*p*-toluidine base in order to stabilize the imidoyl chloride, was performed without success. Under basic conditions, a multivariate screening analysis of the following variables was performed: solvent (THF, pyridine, MeCN, DMF), temperature, and nature of the electrophile (Tf_2O, TosCl, anhydride, etc.), but in most of the cases, the solubility was an issue.[10] In order to bypass this parameter, we applied the multivariate screening analysis on the 2-benzyl-2,3-BZD-1,4-dione (**8a**), in which the amide at the 1-position is protected by a benzyl moiety. In most of the cases, no reaction was observed. However, under tosylation conditions (TsCl, NaH, DMF), the corresponding N-tosylated compound **11** was obtained in 67% yield, while no O-tosylation was detected (Scheme 4). This lack of reactivity of the carbonyl groups appeared to be the same as for the benzylation reactions, in which no O-benzylated compound was obtained.

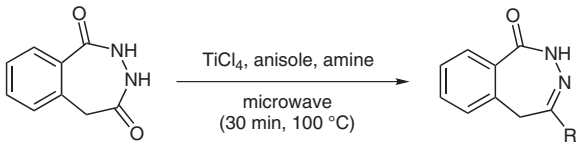


8a **11**

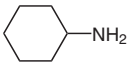
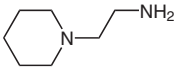
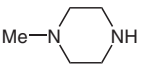
Scheme 4 *Reagents and conditions*: (i) TsCl, NaH, THF, 0 °C, 1 h.

We recently published an efficient microwave-assisted cyclic amidine synthesis using $TiCl_4$.[11] This conversion of an amide into the corresponding amidine involves a two-step one-pot reaction. At first, the amide function interacts with the activated titanium complex to form an imidotitanium adduct, which can be displaced by an amine moiety to yield the corresponding amidine.[12] The microwave-assisted amination of **I** was performed in the presence of 1.2 equivalents of $TiCl_4$ along with 10 equivalents of a primary amine (2-piperidin-1-ylethylamine, cyclohexylamine) or 30 equivalents of a secondary amine (*N*-methylpiperazine, piperidine, morpholine) at 100 °C for 30 minutes (Table 2). A regioselective amination was observed leading to the amidines **12a**–**e**. The amination site at the 4-position was fully characterized by nuclear Overhauser effect (NOE) contact between the methylene group at the 5-position and the protons assignable to methylenes at the α-position of the amine moiety. No amination was detected at the 1-position. The phenylacetamide moiety appeared to be much more reactive toward this $TiCl_4$-mediated amination than the benzamide moiety.

Table 2 Amination of the 2,3-Benzodiazepine-1,4-dione (**I**)



I **12a–e**

Amine (RH)	Equiv	Product	Yield (%)
	30	**12a**	53
	30	**12b**	49
	30	**12c**	50
	10	**12d**	53
	10	**12e**	51

In conclusion, we have shown that an orthogonal protective group strategy applied to hydrazine moiety allowed the synthesis of 2,3-BZD-1,4-dione (**I**) for the first time in a very efficient manner. We next compared the reactivity of both amide functions exhibited by the 2,3-BZD-1,4-dione (**I**). We were able to demonstrate that both nitrogen atoms show an equal nucleophilicity under N-substitution conditions, whereas the phenylacetamide moiety was more reactive than benzamide moiety under $TiCl_4$-mediated amination. This differential reactivity led to a regioselective conversion of the carbonyl at the 4-position of **I** yielding the corresponding amidines **12a**–**e**. Considering the strong interest in drug design of benzodiazepinones in general, we may assume that these efficient syntheses could be used to develop new libraries of 2,3-benzodiazepinone derivatives.

All anhydrous reactions were carried avoiding moisture by standard procedures under argon. Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying agents. Reactions were monitored by TLC inspection on silica gel GF_{254} plates. Column chromatography was generally performed on silica gel (200–300 mesh). All solvent ratios are given as v/v. ^1H, ^{13}C NMR spectra, and NOE experiments were recorded on a Bruker DPX 200 MHz or a Bruker Avance 300 spectrometer. The chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. High-resolution mass spectra (HRMS) and mass spectra (MS) were obtained from a MALDI-TOF and an Agilent 1200SL mass spectrometer, respectively. Melting Points were measured on a Büchi Melting-Point B-540 apparatus. All the microwave reactions were performed with a self-tunable microwave synthesizer (Biotage Initiator EXP microwave apparatus).

The instrument continuously adjusted the wattage automatically to maintain the desired temperature.

3-Methoxyisocoumarine (2)[13]
To a solution of 2-(2-methoxy-2-oxoethyl)benzoic acid (**1**; 200 mg, 1.03 mmol) in degassed anhyd CH_2Cl_2 (5 mL) at 0 °C was added dropwise a solution of trifluoroacetic anhydride (175 μL, 1.24 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 1 h at 0 °C and concentrated in vacuo. The residue was partitioned between EtOAc (20 mL) and H_2O (20 mL). The organic layer was washed with H_2O (2 × 20 mL), aq sat. $NaHCO_3$ (20 mL), and brine (2 × 20 mL), dried (Na_2SO_4), and evaporated in vacuo to yield **2** as a colorless solid (175 mg, 96%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.16 (d, *J* = 7.8 Hz, 1 H, Ar), 7.59 (ddd, *J* = 1.0, 7.3, 7.8 Hz, 1 H, Ar), 7.31–7.26 (m, 2 H, Ar), 5.54 (s, 1 H, H-4), 3.90 (s, 3 H, OCH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 161.5, 160.1, 140.2, 135.4, 130.0, 125.8, 125.0, 117.7, 79.2, 56.4.

MS (ES+): *m*/*z* = 177 $[M + H]^+$.

2-Aminoisoquinoline-1,3(2*H*,4*H*)-dione (3)[4]
To a solution of hydrazine hydrate (153 mg, 149 mL, 1.08 mmol) in EtOH (5 mL) was added homophthalic anhydride (500 mg, 1.08 mmol) and the mixture was refluxed for 6 h. The precipitate was collected and washed with cold EtOH (20 mL). Recrystallization from hot EtOH yielded **3** as a white powder (385 mg, 71%); mp 146 °C (Lit.[4] mp 147–148 °C).

^{1}H NMR (DMSO-d_6, 200 MHz): δ = 8.04 (d, *J* = 7.6 Hz, 1 H, Ar), 7.66 (dd, *J* = 7.6, 7.6 Hz, 1 H, Ar), 7.48 (dd, *J* = 7.6, 7.6 Hz, 1 H, Ar), 7.39 (d, *J* = 7.6 Hz, 1 H, Ar), 5.53 (s, 2 H, NH_2), 4.21 (s, 2 H, H-4).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 167.4, 162.5, 135.5, 134.1, 128.5, 128.4, 128.1, 125.4, 36.7.

MS (ES+): *m*/*z* = 177 $[M + H]^+$.

1-Boc-2-(4-nitrobenzenesulfonyl)hydrazine (4)
To a solution of *tert*-butyl carbazate (3.96 g, 0.30 mol) in anhyd DMF (20 mL) were added K_2CO_3 (4.42 g, 0.32 mol) and 4-nitrobenzenesulfonyl chloride (5.98 g, 0.27 mol). The mixture was stirred for 1 h at r.t. and concentrated in vacuo. The residue was partitioned between EtOAc (40 mL) and aq 1 N HCl (40 mL). The organic layer was washed with aq 1 N HCl (2 × 20 mL), aq sat. $NaHCO_3$ (2 × 20 mL), and brine (2 × 20 mL), dried (Na_2SO_4), and evaporated in vacuo to yield **4** as a yellow powder (7.61 g, 80%); mp 141 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.33 (d, *J* = 9.1 Hz, 2 H, Ar), 8.11 (d, *J* = 9.1 Hz, 2 H, Ar), 6.73 (s, 1 H, NH), 6.65 (s, 1 H, NH), 1.22 (s, 9 H, *t*-C_4H_9).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 154.7, 151.0, 143.2, 130.4, 83.5, 28.2.

ESI-HRMS: *m*/*z* calcd for $C_{11}H_{14}N_3O_6S$ $[M - H]^-$: 316.0608; found: 316.0610.

Hydrazides 7a,b; General Procedure
To a solution of **1** (1.00 g, 5.15 mmol) in anhyd DMF (20 mL) were added HBTU (2.15 g, 5.67 mmol) and Et_3N (1.40 mL, 10.31 mmol). The mixture was stirred for 10 min at r.t. and **4** or **6** (5.67 mmol) was added. The mixture was stirred overnight at r.t. and concentrated in vacuo. The residue was partitioned between EtOAc (40 mL) and aq 1 N HCl (40 mL). The organic layer was washed with aq 1 N HCl (2 × 20 mL), aq sat. $NaHCO_3$ (2 × 20 mL), and brine (2 × 20 mL), dried (Na_2SO_4), and evaporated in vacuo.

[2-(*N*-Benzyl-*N′*-*tert*-butoxycarbonylhydrazinocarbonyl)phenyl]acetic Acid Methyl Ester (7a) Purification by chromatography on silica gel (40% EtOAc in heptane) afforded **7a** as a colorless oil (1.29 g, 63%).

^{1}H NMR (DMSO-d_6, 300 MHz, 130 °C): δ = 8.76 (s, 1 H, NH), 7.39–7.31 (m, 9 H, Ar), 4.71 (s, 2 H, CH_2CO_2Me), 3.71 (s, 2 H, CH_2Ph), 3.62 (s, 3 H, OCH_3), 1.27 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C): δ = 173.0, 172.9, 154.1, 136.8, 136.2, 130.7, 130.4, 129.5, 128.6, 127.8, 127.2, 125.7, 81.3, 52.4, 51.1, 37.9, 28.3.

ESI-HRMS: *m*/*z* calcd for $C_{22}H_{26}N_2O_5Na$ $[M + Na]^+$: 421.1739; found: 421.1730.

{2-[*N*-*tert*-Butoxycarbonyl-*N′*-(4-nitrobenzenesulfonyl)hydrazinocarbonyl)]phenyl}acetic Acid Methyl Ester (7b)
Purification by chromatography on silica gel (40% EtOAc in heptane) afforded **7b** as a yellow oil (2.12 g, 85%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.49 (d, *J* = 9.1 Hz, 2 H, Ar), 8.40 (d, *J* = 9.1 Hz, 2 H, Ar), 7.75 (s, 1 H, NH), 7.38–7.32 (m, 3 H), 7.22 (d, *J* = 7.5 Hz, 1 H, Ar), 3.92 (s, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 1.42 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 172.5, 170.7, 153.4, 150.6, 143.2, 133.5, 130.9, 130.7, 130.5, 126.7, 125.4, 123.4, 82.6, 52.3, 37.4, 27.7.

ESI-HRMS: *m*/*z* calcd for $C_{21}H_{23}N_3O_9SNa$ $[M + Na]^+$: 516.1053; found: 516.1077.

Cleavage of Boc Protected 7a,b and Cyclization to 8a,b; General Procedure
To a solution of **7a** or **7b** (3.26 mmol) in anhyd CH_2Cl_2 (10 mL) was added trifluoroacetic acid (10 mL). The mixture was stirred for 1 h at r.t. and concentrated in vacuo. Et_2O (5 mL) was added and sonication of the resulting solution for 60 s afforded a white solid which was filtered and dried at reduced pressure to yield **8a** or **8b** as white powders.

2-Benzyl-2,3-dihydro-5*H*-2,3-benzodiazepine-1,4-dione (8a)
Yield: 764 mg (88%); mp 143 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.17 (br s, 1 H, NH), 7.92 (dd, *J* = 1.5, 6.8 Hz, 1 H, Ar), 7.49–7.42 (m, 2 H, Ar), 7.38–7.31 (m, 5 H, Ar), 7.20 (dd, *J* = 1.5, 6.8 Hz, 1 H, Ar), 4.96 (dd, *J* = 14.0, 127 Hz, 2 H, CH_2Ph), 3.48 (dd, *J* = 13.0, 169 Hz, 2 H, CH_2CO).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.8, 169.0, 136.3, 135.4, 132.9, 130.8, 129.4, 128.9, 128.7, 128.6, 52.7, 41.0.

ESI-HRMS: *m*/*z* calcd for $C_{16}H_{14}N_2O_2Na$ $[M + Na]^+$: 289.0953; found: 289.0939.

2-(4-Nitrobenzenesulfonyl)-2,3-dihydro-5*H*-2,3-benzodiazepine-1,4-dione (8b)
Yield: 1.08 g (92%); mp 241 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 10.87 (s, 1 H, NH), 8.53 (d, *J* = 9.0 Hz, 2 H, Ar), 8.44 (d, *J* = 9.0 Hz, 2 H, Ar), 7.81 (dd, *J* = 1.5, 7.5 Hz, 1 H, Ar), 7.66 (ddd, *J* = 1.5, 7.5, 7.5 Hz, 1 H, Ar), 7.50 (m, 2 H, Ar), 3.87 (dd, *J* = 13.0, 225 Hz, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.7, 167.5, 151.8, 143.8, 137.4, 135.3, 131.7, 131.2, 130.6, 130.2, 129.4, 125.5, 41.0.

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{10}N_3O_6S$ $[M - H]^-$: 360.0290; found: 360.0294.

2,3-Dihydro-5*H*-2,3-benzodiazepine-1,4-dione (I)
By Cleavage of the Nosyl Group: To a solution of **8b** (1.00 g, 2.77 mmol) in anhyd DMF (5 mL) were added Cs_2CO_3 (2.70 g, 8.31 mmol) and thiophenol (311 μL, 3.05 mmol). The mixture was stirred for 3 h at r.t., and concentrated in vacuo. The resulting crude product was dissolved in a solution of 5% MeOH in CH_2Cl_2, filtered

and purified by chromatography on silica gel (5% MeOH in CH_2Cl_2 + 1% AcOH) to yield **I** as a white powder (370 mg, 76%).

By Cleavage of the Benzyl Group: To a solution of **8a** (40 mg, 0.15 mmol) in EtOAc (4 mL) and AcOH (1 mL) was added $PdCl_2$ (3.00 mg, 10% mol). The mixture was hydrogenated at r.t. at 60 psi. After 24 h, the mixture was filtered and evaporated in vacuo. The resulting crude product was dissolved in EtOAc (10 mL) and washed with brine (2 × 5 mL), dried (Na_2SO_4), and evaporated in vacuo. Purification was performed by chromatography on silica gel (5% MeOH in CH_2Cl_2 + 1% AcOH) to yield **I** as a white powder (7 mg, 26%); mp 185 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 10.19 (s, 1 H, NH), 9.78 (s, 1 H, NH), 7.72 (dd, *J* = 1.6, 7.5 Hz, 1 H, Ar), 7.53 (ddd, *J* = 1.6, 7.5, 7.5 Hz, 1 H, Ar), 7.43 (ddd, *J* = 1.3, 7.5, 7.5 Hz, 1 H, Ar), 7.37 (d, *J* = 7.5 Hz, 1 H, Ar), 3.66 (dd, *J* = 13.0, 242 Hz, 2 H, CH_2).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 173.5, 169.1, 136.6, 132.1, 131.8, 129.4, 128.4, 127.6, 40.8.

ESI-HRMS: *m*/*z* calcd for $C_9H_8N_2O_2SNa$ [M + Na]$^+$: 199.0483, found: 199.0490.

Benzylation of 2,3-Dihydro-5*H*-2,3-benzodiazepine-1,4-dione (I)

Method A: To a solution of **I** (20.0 mg, 0.11 mmol) in anhyd DMF (1 mL) at 0 °C was added a dispersion of NaH (60%, 3.00 mg, 0.08 mmol) and the mixture was stirred for 10 min at 0 °C. Then, benzyl bromide (20.0 mg, 14.0 μL, 0.08 mmol) was quickly added and the mixture was stirred for 1 h at r.t., and concentrated in vacuo. The residue was partitioned between EtOAc (20 mL) and H_2O (20 mL). The organic layer was washed with brine (2 × 20 mL), dried (Na_2SO_4), and evaporated in vacuo. Purification by chromatography on silica gel (25% to 50% EtOAc in heptane) afforded the compounds **8a**, **9**, and **10** in 22% (4.0 mg), 22% (4.0 mg), and 56% (8.0 mg) yield, respectively.

Method B: To a solution of **I** (19.0 mg, 0.11 mmol) in anhyd DMF (2 mL) at 0 °C was added K_2CO_3 (55.00 mg, 0.28 mmol) and the mixture was stirred for 10 min at 0 °C. Then, benzyl bromide (11.0 μL, 0.09 mmol) was quickly added and the mixture was stirred for 1 h at r.t., and concentrated in vacuo. The residue was partitioned between EtOAc (20 mL) and H_2O (20 mL). The organic layer was washed with brine (2 × 20 mL), dried (Na_2SO_4), and evaporated in vacuo. Purification by chromatography on silica gel (25% to 50% EtOAc in heptane) afforded the compounds **8a**, **9**, and **10** in 24% (6.0 mg), 20% (5.0 mg), and 53% (9.0 mg) yield, respectively.

Method C: To a solution of **I** (20.0 mg, 0.11 mmol) in anhyd DMF (2 mL) at 0 °C was added a dispersion of NaH (60%, 9.0 mg, 0.0.22 mmol) and the mixture was stirred for 10 min at 0 °C. Then, benzyl bromide (28.0 μL, 0.22 mmol) was quickly added and the mixture was stirred for 1 h at r.t., and concentrated in vacuo. The residue was partitioned between EtOAc (20 mL) and H_2O (20 mL). The organic layer was washed with brine (2 × 20 mL), dried (Na_2SO_4), and evaporated in vacuo. Purification by chromatography on silica gel (25% to 50% EtOAc in heptane) afforded the compound **10** in 89% (36.0 mg) yield.

3-Benzyl-2,3-dihydro-5*H*-2,3-benzodiazepine-1,4-dione (9)

Mp 162 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.70 (s, 1 H, NH), 7.65 (dd, *J* = 1.3, 7.8 Hz, 1 H, Ar), 7.53 (ddd, *J* = 1.3, 7.5, 7.8 Hz, 1 H, Ar), 7.38 (dd, *J* = 7.5, 7.5 Hz, 1 H, Ar), 7.33 (d, *J* = 7.5 Hz, 1 H, Ar), 7.31–7.24 (m, 3 H, Ar), 7.10 (dd, *J* = 1.6, 7.5 Hz, 2 H, Ar), 4.72 (dd, *J* = 14.0, 37 Hz, 2 H, C*H*$_2$Ph), 3.90 (dd, *J* = 13.0, 209 Hz, 2 H, CH_2CO).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.0, 173.4, 139.2, 137.2, 136.6, 133.7, 133.2, 132.4, 132.2, 131.9, 131.5, 55.6, 45.3.

ESI-HRMS: *m*/*z* calcd for $C_{16}H_{14}N_2O_2Na$ [M + Na]$^+$: 289.0953; found: 289.0945.

2,3-Dibenzyl-2,3-dihydro-5*H*-2,3-benzodiazepine-1,4-dione (10)

Mp 119 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.36–7.25 (m, 6 H, Ar), 7.19–7.13 (m, 3 H, Ar), 7.02–6.94 (m, 3 H, Ar), 6.71 (d, *J* = 7.2 Hz, 2 H, Ar), 4.87 (dd, *J* = 14.0, 392 Hz, 2 H, C*H*$_2$Ph), 4.65 (dd, *J* = 14.0, 374 Hz, 2 H, C*H*$_2$Ph), 3.30 (dd, *J* = 13.0, 156 Hz, 2 H, CH_2CO).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.4, 170.0, 136.0, 14.9, 134.2, 132.5, 131.7, 129.9, 129.7, 129.5, 129.4, 128.9, 128.6, 128.4, 128.2, 128.1, 49.4, 48.8, 41.3.

ESI-HRMS: *m*/*z* calcd for $C_{23}H_{20}N_2O_2Na$ [M + Na]$^+$: 379.1422; found: 379.1408.

2-Benzyl-3-(*p*-toluenesulfonyl)-2,3-dihydro-5*H*-benzodiazepine-1,4-dione (11)

To a solution of **8a** (400 mg, 1.5 mmol) in anhyd THF (20 mL) was added NaH (60% suspension in mineral oil; 78 mg, 1.95 mmol) at 0 °C and the mixture was stirred for 30 min at 0 °C. Then, tosyl chloride (342 mg, 1.80 mmol) was quickly added and the mixture was stirred for 1 h and concentrated in vacuo. The residue was partitioned between EtOAc (20 mL) and H_2O (20 mL). The organic layer was washed with brine (2 × 20 mL), dried (Na_2SO_4), and evaporated in vacuo. Purification by chromatography on silica gel (10% to 50% EtOAc in heptane) afforded **8** as a colorless oil, which was dissolved in Et_2O and sonicated to yield **11** as a white powder (420 mg, 67%); mp 155 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.79 (dd, *J* = 1.5, 7.3 Hz, 1 H), 7.35 (m, 9 H), 7.00 (d, *J* = 8.3 Hz, 2 H), 6.84 (d, *J* = 7.3 Hz, 1 H), 5.16 (dd, *J* = 14.0, 305 Hz, 2 H), 3.20 (dd, *J* = 13.0, 122 Hz, 2 H), 2.30 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.4, 169.1, 146.2, 135.3, 133.2, 132.9, 132.5, 131.3, 130.7, 130.5, 130.2, 130.1, 129.8, 129.6, 129.5, 129.2, 129.1, 128.9, 54.1, 42.3, 22.0.

ESI-HRMS: *m*/*z* calcd for $C_9H_8N_2O_2SNa$ [M + Na]$^+$: 443.1041; found: 443.1039.

Amination of 2,3-Dihydro-5*H*-2,3-benzodiazepine-1,4-dione (I); General Procedure

To a 1 M solution of $TiCl_4$ in CH_2Cl_2 (250 μL, 0.25 mmol) was added anisole (700 μL) under argon and the mixture was stirred for 15 min. Then, amine (10 equiv for a primary amine, 30 equiv for a secondary amine) and **I** (38.2 mg, 0.21 mmol) were added and the mixture was irradiated under microwave at 100 °C for 30 min and was partitioned between EtOAc (20 mL) and aq sat. $NaHCO_3$ (20 mL). The organic layer was washed with aq sat. $NaHCO_3$ (2 × 20 mL), and brine (2 × 20 mL), dried (Na_2SO_4), and evaporated in vacuo. Purification by chromatography on silica gel (5% MeOH in CH_2Cl_2 + 1% AcOH) afforded the expected amidine.

4-(4-Methylpiperazin-1-yl)-2,5-dihydro-1*H*-2,3-benzodiazepin-1-one (12a)

Yield: 28.0 mg (53%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.39 (s, 1 H, NH), 8.00 (dd, *J* = 1.5, 7.6 Hz, 1 H, Ar), 7.48–7.41 (m, 2 H, Ar), 7.17 (d, *J* = 7.6 Hz, 1 H), 3.73 (s, 2 H, CH_2C=N), 3.38 (t, *J* = 4.9 Hz, 4 H, 2 × CH_2N), 2.41 (t, *J* = 4.9 Hz, 4 H, 2 × CH_2N), 2.28 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.3, 162.9, 136.9, 132.9, 132.5, 131.1, 128.1, 127.0, 54.8, 46.5, 46.4, 33.7.

ESI-HRMS: *m*/*z* calcd for $C_{14}H_{19}N_4O$ [M + H]$^+$: 259.1559; found: 259.1548.

4-(Piperidin-1-yl)-2,5-dihydro-1*H*-2,3-benzodiazepin-1-one (12b)
Yield: 27.0 mg (49%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.30 (br s, 1 H, NH), 8.07 (dd, *J* = 1.2, 7.6 Hz, 1 H), 7.53 (dd, *J* = 1.7, 7.3 Hz, 1 H, Ar), 7.42 (dd, *J* = 1.2, 7.3 Hz, 1 H, Ar), 7.22 (d, *J* = 7.6 Hz, 1 H, Ar), 3.42–3.19 (m, 6 H, 3 × CH_2), 2.53–2.39 (m, 4 H, 2 × CH_2), 1.61–1.54 (m, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.1, 163.2, 140.5, 133.3, 131.6, 129.0, 128.4, 58.6, 55.2, 48.6, 30.1, 26.1.

ESI-HRMS: *m*/*z* calcd for $C_{14}H_{18}N_3O$ $[M + H]^+$: 244.1444; found: 244.1441.

4-(Morpholin-1-yl)-2,5-dihydro-1*H*-2,3-benzodiazepin-1-one (12c)
Yield: 25.0 mg (50%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.52 (br s, 1 H, NH), 8.01 (dd, *J* = 1.6, 7.6 Hz, 1 H, Ar), 7.50 (dd, *J* = 1.6, 7.5 Hz, 1 H, Ar), 7.41 (dd, *J* = 1.2, 7.8 Hz, 1 H, Ar), 7.16 (d, *J* = 7.5 Hz, 1 H, Ar), 3.72 (s, 2 H, CH_2C=N), 3.71 (t, *J* = 4.7 Hz, 4 H, 2 × CH_2), 3.33 (t, *J* = 4.7 Hz, 4 H, 2 × CH_2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 167.7, 161.5, 135.3, 131.5, 129.7, 126.7, 125.5, 65.6, 45.6, 32.1.

ESI-HRMS: *m*/*z* calcd for $C_{13}H_{16}N_3O_2$ $[M + H]^+$: 246.1237; found: 246.1235.

4-[(2-Piperidin-1-ylethyl)amino]-2,5-dihydro-1*H*-2,3-benzodiazepin-1-one (12d)
Yield: 32.0 mg (53%).

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 9.92 (s, 1 H, NHCO), 7.72 (d, *J* = 7.5 Hz, 1 H, Ar), 7.50 (dd, *J* = 7.5, 7.5 Hz, 1 H, Ar), 7.37 (dd, *J* = 7.5, 7.5 Hz, 1 H, Ar), 7.23 (d, *J* = 7.5 Hz, 1 H, Ar), 6.93 (br s, 1 H, N*H*CH_2), 3.55 (s, 2 H, CH_2C=N), 3.21 (m, 2 H, CH_2NH), 2.67 (m, 4 H, 2 × CH_2N), 1.43 (m, 8 H, 4 × CH_2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.3, 161.2, 137.4, 132.9, 132.2, 130.6, 128.0, 127.9, 56.5, 54.4, 38.0, 37.5, 24.5, 23.5.

ESI-HRMS: *m*/*z* calcd for $C_{16}H_{23}N_4O$ $[M + H]^+$: 287.1872; found: 287.1885.

4-Cyclohexylamino-2,5-dihydro-1*H*-benzodiazepin-1-one (12e)
Yield: 28.0 mg (51%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.32 (br s, 1 H, NHCO), 8.01 (dd, *J* = 1.7, 7.3 Hz, 1 H), 7.52 (dd, *J* = 1.5, 7.6 Hz, 1 H, Ar), 7.42 (dd, *J* = 1.2, 7.3 Hz, 1 H, Ar), 7.17 (d, *J* = 7.6 Hz, 1 H, Ar), 4.39 (br s, 1 H, NH), 3.55 (s, 2 H, CH_2C=N), 3.50–3.40 (m, 1 H, CH), 2.04–1.90 (m, 2 H, CH_2), 1.77–1.56 (m, 4 H, 2 × CH_2), 1.37–1.21 (m, 2 H, CH_2), 1.20–1.04 (m, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.4, 160.1, 137.3, 132.8, 132.3, 130.9, 128.2, 127.4, 50.7, 39.0, 33.2, 26.1, 25.2.

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{20}N_3O$ $[M + H]^+$: 258.1601; found 258.1608.

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