Synthesis of 1,4-Benzodiazepine-2,5-diones Using an Ionic Liquid as a Soluble Support

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Abstract: The first report of the use of an ionic liquid as a soluble support for the synthesis of 1,4-benzodiazepine-2,5-diones is reported in this paper. This synthetic method is simple and efficient and the products are obtained in good yields. All of the products were characterized by IR, ^{1}H NMR, and ^{13}C NMR.

Key words: ionic liquid, synthesis, 1,4-benzodiazepine-2,5-diones, soluble support

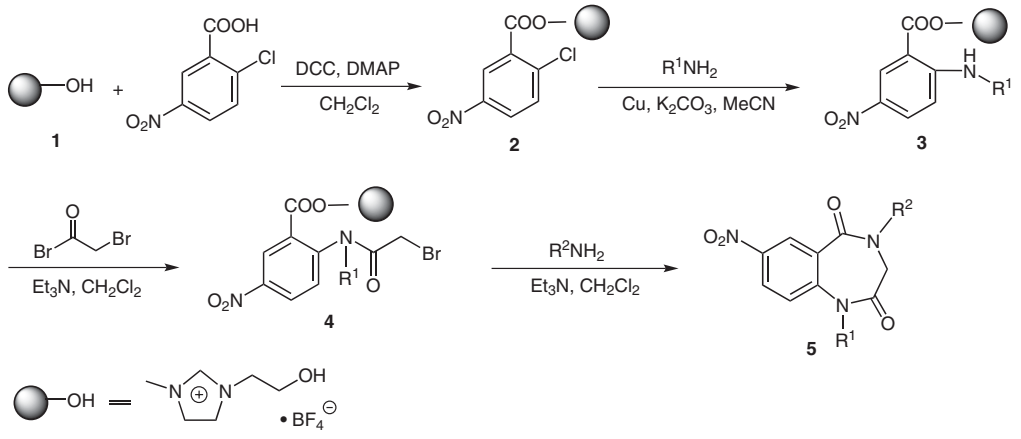
1,4-Benzodiazepine-2,5-dione and its analogues represent an important class of bioactive molecules. These compounds show remarkable potency in various biological targets, including antithrombotic, antibiotic, and antitumor activity.[1] Much effort has been exerted in the synthesis of this class of bioactive compounds.[1,2] The combinatorial or parallel synthetic approaches are especially noted.[2]

Using a polymer as a support in combinatorial chemistry has become an efficient tool to build small molecule libraries to accelerate the drug discovery process. In the field of combinatorial chemistry, solid-phase organic synthesis (SPOS) has been accepted as an efficient method for high-throughput synthesis.[3] Despite its great success, solid-phase synthesis still exhibits several shortcomings such as the nature of the heterogeneous reaction and difficulties in reaction monitoring. By replacing insoluble cross-linked resins with soluble polymer supports, the familiar reaction conditions of classical organic chemistry are reinstated and, yet, product purification is still facilitated due to their macromolecular properties.[4] Noncrosslinked polystyrene and poly(ethylene glycol) (PEG) are the most common and useful soluble polymers for liquid-phase organic synthesis,[5] however, the main limitation of soluble polymer supports is low loading capacity. Hence, the idea of searching for alternative soluble supports for high-throughput organic synthesis has been advocated.

Recently, more attention within the realm of room temperature ionic liquid research has been paid to ionic liquids with special tasks.[6] Ionic liquids have been introduced as soluble supports in liquid-phase organic synthesis;[7] they have the advantages of retaining the nature of a homogeneous reaction, high loading capacity, a wide range of solvents, simple monitoring technology, and low cost.

Having the above facts in mind and, as a part of our continuing efforts to develop liquid-phase methods on soluble supports for the synthesis of heterocyclic compounds,[8] we herein report a new synthetic approach to 1,4-benzodiazepine-2,5-diones using an ionic liquid as a soluble support (Scheme 1).

As shown in Scheme 1, ionic liquid 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate ([2-hydemim]



Scheme 1

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[BF_4], **1**) was reacted with 2-chloro-5-nitrobenzoic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide and a catalytic amount of 4-(dimethylamino)pyridine in dry dichloromethane to offer ionic-liquid-supported carboxylic ester **2**. The appearance of the ester carbonyl at 1715 cm^{-1} in the IR spectrum is a clear evidence for the formation of **2**. The intermediate **2** was treated with a series of aliphatic amines to afford ionic-liquid-supported amino esters **3**. An array of experiments carried out with different reaction temperatures and times, the optimal results were obtained by refluxing in acetonitrile at 80 °C for five hours. Amino esters **3** were treated with bromoacetyl bromide in the presence of triethylamine to afford ionic-liquid-supported amide esters **4**. Subsequently, consistent cyclization/cleavage of **4** to give **5** was achieved by treatment of **4** with a variety of aliphatic amines in the presence of triethylamine. On completion of the reaction, the crude products were purified by flash chromatography on silica gel to afford 1,4-benzodiazepine-2,5-diones **5**. The purified products were characterized by conventional techniques (^1H and ^{13}C NMR and IR). As shown in Table 1, our method was found to be generally applicable, all the products were obtained in good overall yields. It is worthy of note that, in each step of the sequence, the ionic-liquid-supported intermediates were purified by washing with diethyl ether. The excess reaction reagents and the byproducts were removed by simple decantation. Moreover, the ionic liquid [2-hydemim][BF_4] (**1**) could be typically recovered (the yield of recovered **1** was ≥92%) and reused with no appreciable decrease in yields and reaction rates.

In summary, we report an efficient and new route for the synthesis of 1,4-benzodiazepine-2,5-diones using an ionic liquid as a soluble support. The use of this novel ionic liquid support offers many advantages compared to previously reported methods including environmental friendliness, much higher loading capacity, easy isolation and purification of the products, shorter reaction times, higher yields, no need for use of large excess of reagents, compatibility with automatic manipulation, use of standard analytical methods (IR, NMR, TLC) to monitor reaction progress, and recyclability of the soluble support. To our knowledge, this methodology has not previously been reported for the preparation of these 1,4-benzodiazepine-2,5-diones and may complement existing methods in the literature. We are currently exploring the scope and potential of the ionic liquid by extending this methodology to other heterocyclic targets.

All organic solvents and bases were dried by standard methods. TLCs were performed on precoated plates of silica gel HF254 (0.5 mm, Yantai, China). Flash column chromatography was performed on silica gel H (Yantai, China). Melting points were measured on a WRS-1A digital melting point apparatus and uncorrected. IR spectra were recorded on an IR spectrum one (PE) spectrophotometer, ^1H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Varian Unity Inova 600 spectrometer in $CDCl_3$ using TMS as internal standard. Element analysis was determined by a Vario EL III (Germany) analyzer.

Table 1 Synthesis of 1,4-Benzodiazepine-2,5-diones Using an Ionic Liquid as a Soluble Support

Product	R^1	R^2	Overall yield (%) from **1**
5a	Pr	Pr	71
5b		Bu	69
5c		$(CH_2)_4Me$	71
5d		$(CH_2)_5Me$	71
5e		$(CH_2)_2Ph$	68
5f	Bu	Pr	67
5g		Bu	66
5h		$(CH_2)_4Me$	69
5i		$(CH_2)_5Me$	68
5j		$(CH_2)_2Ph$	70
5k	$(CH_2)_4Me$	Pr	67
5l		Bu	67
5m		$(CH_2)_4Me$	66
5n		$(CH_2)_5Me$	64
5o		$(CH_2)_2Ph$	62
5p	$(CH_2)_5Me$	Pr	63
5q		Bu	62
5r		$(CH_2)_4Me$	65
5s		$(CH_2)_5Me$	64
5t		$(CH_2)_2Ph$	61
5u	$(CH_2)_2Ph$	Pr	62
5v		Bu	68
5w		$(CH_2)_4Me$	67
5x		$(CH_2)_5Me$	64
5y		$(CH_2)_2Ph$	66

Ionic-Liquid-Supported Carboxylic Ester 2

2-Chloro-5-nitrobenzoic acid (3.5 g, 17.5 mmol), DCC (3.09 g, 15 mmol), and DMAP (0.09 g, 0.75 mmol) were added to a soln of [2-hydemim][BF_4] **1** (3.2 g, 15 mmol) in CH_2Cl_2 (70 mL). After vigorous stirring at r.t. for 12 h, insoluble *N*,*N*′-dicyclohexylurea was removed by filtration. The filtrate was concentrated under reduced pressure and the resulting crude mixture was washed with anhyd Et_2O (3 × 20 mL) and dried under vacuum to give **2** as a yellow viscous oil in 97% yield.

IR (NaCl): 1715 cm^{-1}.

^1H NMR (600 MHz, CD_3Cl): δ = 3.89 (t, 2 H, NCH_2), 4.06 (s, 3 H, NCH_3), 4.39 (t, 2 H, $NCCH_2$), 7.63 (t, *J* = 1.6 Hz, 1 H, H4), 7.67 (d, 1 H, Ph-H3), 7.70 (t, *J* = 1.6 Hz, 1 H, H5), 8.35 (d, 1 H, Ph-H4), 8.82 (s, 1 H, Ph-H6), 8.88 (s, 1 H, NCHN).

Ionic-Liquid-Supported Amino Esters 3; General Procedure

To a soln of **2** (2.0 g, 5 mmol), K_2CO_3 (0.96 g, 7 mmol), and Cu powder (0.02 g, 0.25 mmol) in MeCN (20 mL) was added dropwise a soln of aliphatic amine (7 mmol) in MeCN (5 mL). The mixture was stirred at 80 °C for 5 h and then cooled to r.t. and filtered. The filtrate was concentrated under reduced pressure and the resulting crude mixture was washed with anhyd Et_2O (3 × 20 mL) and dried under vacuum to give **3**.

3a

IR (NaCl): 3279, 1711 cm^{-1}.

^1H NMR (600 MHz, CD_3Cl): δ = 0.94 (t, 3 H, CH_3), 1.58 (m, 2 H, CH_2), 3.09 (m, 2 H, CH_2), 3.63 (s, 3 H, NCH_3), 3.92 (t, 2 H, CH_2), 4.01 (t, 1 H, NH), 4.38 (t, 2 H, CH_2), 6.80 (d, *J* = 1.6 Hz, 1 H, Ph-H3), 7.66–7.69 (d, 2 H, H4, H5), 8.23 (d, 1 H, Ph-H4), 8.78 (s, 1 H, Ph-H6), 8.93 (s, 1 H, NCHN).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.53, 23.32, 37.91, 47.33, 55.52, 62.11, 108.32, 114.32, 122.81, 123.03, 125.62, 126.21, 136.73, 137.32, 155.81, 166.13.

Ionic-Liquid-Supported Amide Esters 4; General Procedure

To a vigorously stirred soln of **3** (3.0 mmol) and Et_3N (0.7 mL, 5 mmol) in anhyd CH_2Cl_2 (20 mL) was added dropwise a soln of freshly distilled 2-bromoacetyl bromide (0.45 mL, 5 mmol) in anhyd CH_2Cl_2 (10 mL) over 15 min at ice-bath temperature; the mixture was then refluxed at 40 °C for 12 h. The solvent was evaporated and the crude mixture was washed with anhyd Et_2O (3 × 10 mL) and dried under vacuum to afford **4**.

4a

IR (NaCl): 3374, 1712 cm^{-1}.

^{1}H NMR (600 MHz, CD_3Cl): δ = 0.96 (t, 3 H, CH_3), 1.48 (m, 2 H, CH_2), 3.36 (t, 2 H, CH_2), 3.63 (s, 3 H, NCH_3), 3.91 (t, 2 H, CH_2), 4.24 (s, 1 H, COCHBr), 4.36 (t, 2 H, CH_2), 7.47 (d, 1 H, Ph-H3), 7.63–7.68 (d, 2 H, H4, H5), 8.44 (d, 1 H, Ph-H4), 8.81 (s, 1 H, NCHN), 8.95 (s, 1 H, Ph-H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.52, 20.41, 26.43, 37.92, 41.91, 55.73, 62.32, 116.61, 122.63, 122.82, 123.21, 125.23, 125.62, 137.21, 143.93, 147.62, 166.21, 166.53.

1,4-Benzodiazepine-2,5-diones 5; General Procedure

To a soln of **4** (5 mmol) and Et_3N (1.2 mL, 8.6 mmol) in CH_2Cl_2 (10 mL) was added dropwise a soln of aliphatic amine (10 mmol) in CH_2Cl_2 (5 mL). Then the liquid mixture was stirred mechanically and refluxed at 40 °C for 12 h. The resulting soln was concentrated and the crude soln was purified by flash chromatography (silica gel, *n*-hexane–EtOAc, 4:1) to give the products **5a**–**y**.

7-Nitro-1,4-dipropyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5a)

Mp 121.3–122.5 °C.

IR (NaCl): 1689, 1654, 1526, 1344 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.95 (t, 6 H, CH_3), 1.41–1.65 (m, 4 H, CH_2), 3.18 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.30 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.12 (s, 2 H, H3), 7.36 (d, *J* = 7.8 Hz, 1 H, H9), 8.34 (d, *J* = 7.8 Hz, 1 H, H8), 8.81 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.12, 11.14, 20.25, 20.51, 46.34, 48.91, 51.38, 122.42, 126.44, 127.16, 130.93, 144.46, 144.48, 164.84, 167.72.

Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. Found: C, 58.92; H, 6.32; N, 13.65.

4-Butyl-7-nitro-1-propyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5b)

Mp 120.5–121.6 °C.

IR (NaCl): 1688, 1653, 1526, 1343 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.95 (t, 6 H, CH_3), 1.33–1.60 (m, 6 H, CH_2), 3.21 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.39 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.14 (s, 2 H, H3), 7.55 (d, *J* = 7.8 Hz, 1 H, H9), 8.50 (d, *J* = 7.8 Hz, 1 H, H8), 8.92 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.13, 13.56, 20.23, 20.50, 28.61, 46.35, 48.91, 51.36, 122.41, 126.45, 127.17, 130.92, 144.46, 144.49, 164.85, 167.74.

Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.17; H, 6.63; N, 13.16. Found: C, 60.04; H, 6.67; N, 13.12.

7-Nitro-4-pentyl-1-propyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5c)

Mp 114.3–116.5 °C.

IR (NaCl): 1688, 1652, 1527, 1346 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.95 (t, 6 H, CH_3), 1.30–1.60 (m, 8 H, CH_2), 3.21 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.39 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.28 (s, 2 H, H3), 7.40 (d, *J* = 7.8 Hz, 1 H, H9), 8.34 (d, *J* = 7.8 Hz, 1 H, H8), 8.79 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.10, 13.97, 19.77, 22.32, 27.24, 28.77, 46.90, 48.92, 51.41, 122.43, 126.44, 127.16, 130.93, 144.49, 144.48, 164.88, 167.75.

Anal. Calcd for $C_{17}H_{23}N_3O_4$: C, 61.25; H, 6.95; N, 12.60. Found: C, 61.12; H, 6.92; N, 12.58.

4-Hexyl-7-nitro-1-propyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5d)

Mp 98.5–99.1 °C.

IR (NaCl): 1688, 1653, 1526, 1344 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.96 (t, 6 H, CH_3), 1.2–1.69 (m, 10 H, CH_2), 3.21 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.39 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.18 (s, 2 H, H3), 7.40 (d, *J* = 7.8 Hz, 1 H, H9), 8.34 (d, *J* = 7.8 Hz, 1 H, H8), 8.79 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.12, 13.56, 19.98, 22.41, 27.34, 28.78, 29.76, 46.93, 48.91, 51.38, 122.39, 126.41, 127.20, 130.90, 144.43, 144.47, 164.87, 167.71.

Anal. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.23; H, 7.25; N, 12.10. Found: C, 62.12; H, 7.31; N, 12.05.

7-Nitro-4-phenethyl-1-propyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5e)

Mp 54.4–55.3 °C.

IR (NaCl): 1689, 1655, 1527, 1344 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.90 (t, 3 H, CH_3), 1.48 (t, 2 H, CH_2), 3.0 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.65 (t, *J* = 7.2 Hz, 2 H), 3.91 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.20 (s, 2 H, H3), 7.21–7.31 (m, 5 H), 7.38 (d, *J* = 7.8 Hz, 1 H, H9), 8.33 (d, *J* = 7.8 Hz, 1 H, H8), 8.74 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.21, 21.32, 29.93, 34.21, 49.03, 50.81, 122.32, 122.61, 122.81, 126.73, 126.91, 127.32, 128.23, 128.31, 128.52, 137.92, 144.53, 144.71, 165.12, 167.83.

Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.29; H, 5.80; N, 11.46.

1-Butyl-7-nitro-4-propyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5f)

Mp 123.1–124.2 °C.

IR (NaCl): 1688, 1653, 1527, 1345 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.96 (t, 6 H, CH_3), 1.33–1.63 (m, 6 H, CH_2), 3.27 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.49 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.16 (s, 2 H, H3), 7.46 (d, *J* = 7.8 Hz, 1 H, H9), 8.38 (d, *J* = 7.8 Hz, 1 H, H8), 8.81 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.10, 13.87, 19.78, 20.01, 28.76, 46.89, 48.92, 51.34, 122.39, 126.40, 127.15, 130.89, 144.42, 144.50, 164.85, 167.71.

Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.17; H, 6.63; N, 13.16. Found: C, 60.11; H, 6.72; N, 13.20.

1,4-Dibutyl-7-nitro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5g)

Mp 102.1–104.2 °C.

IR (NaCl): 1689, 1651, 1525, 1340 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.95 (t, 6 H, CH_3), 1.32–1.59 (m, 8 H, CH_2), 3.25 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.42 (t, *J* = 7.2 Hz, 2 H,

CH_2), 4.16 (s, 2 H, H3), 7.58 (d, J = 7.8 Hz, 1 H, H9), 8.53 (d, J = 7.8 Hz, 1 H, H8), 8.91 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.51, 13.67, 19.75, 19.90, 29.58, 29.73, 46.92, 48.71, 51.40, 122.41, 126.40, 127.12, 130.92, 144.49, 144.69, 164.86, 167.73.

Anal. Calcd for $C_{17}H_{23}N_3O_4$: C, 61.25; H, 6.95; N, 12.60. Found: C, 61.12; H, 7.07; N, 12.57.

1-Butyl-7-nitro-4-pentyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5h)
Mp 102.1–104.2 °C.

IR (NaCl): 1689, 1652, 1525, 1344 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.96 (t, 6 H, CH_3), 1.24–1.69 (m, 10 H, CH_2), 3.25 (t, J = 7.2 Hz, 2 H, CH_2), 3.50 (t, J = 7.2 Hz, 2 H, CH_2), 4.14 (s, 2 H, H3), 7.40 (d, J = 7.8 Hz, 1 H, H9), 8.44 (d, J = 7.8 Hz, 1 H, H8), 8.83 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.55, 13.97, 19.78, 22.31, 27.24, 28.76, 29.74, 46.91, 48.90, 51.39, 122.41, 126.41, 127.14, 130.99, 144.43, 144.46, 164.86, 167.73.

Anal. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.23; H, 7.25; N, 12.10. Found: C, 62.06; H, 7.34; N, 12.06.

1-Butyl-4-hexyl-7-nitro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5i)
Mp 75.1–76.1 °C.

IR (NaCl): 1687, 1652, 1525, 1343 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.96 (t, 6 H, CH_3), 1.28–1.60 (m, 12 H, CH_2), 3.25 (t, J = 7.2 Hz, 2 H, CH_2), 3.50 (t, J = 7.2 Hz, 2 H, CH_2), 4.15 (s, 2 H, H3), 7.42 (d, J = 7.8 Hz, 1 H, H9), 8.54 (d, J = 7.8 Hz. 1 H, H8), 8.89 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.55, 13.97, 19.86, 22.32, 26.84, 27.24, 28.76, 31.34, 46.89, 48.88, 51.37, 122.40, 126.41, 127.12, 130.90, 144.45, 144.45, 164.86, 167.74.

Anal. Calcd for $C_{19}H_{27}N_3O_4$: C, 63.14; H, 7.53; N, 11.63. Found: C, 63.08; H, 7.55; N, 11.60.

1-Butyl-7-nitro-4-phenethyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5j)
IR (NaCl): 1688, 1653, 1526, 1344 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.95 (t, 3 H, CH_3), 1.21–1.57 (m, 4 H, CH_2), 2.98 (t, J = 7.2 Hz, 2 H, CH_2), 3.42 (t, J = 7.2 Hz, 2 H, CH_2), 3.66 (t, J = 7.2 Hz, 2 H, CH_2), 4.23 (s, 2 H, H3), 7.21–7.34 (m, 5 H), 7.38 (d, J = 7.8 Hz, 1 H, H9), 8.32 (d, J = 7.8 Hz, 1 H, H8), 8.84 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.52, 19.83, 29.71, 33.92, 46.93, 50.51, 51.92, 126.52, 126.73, 127.11, 128.22, 128.33, 128.51, 128.62, 128.83, 130.71, 137.82, 144.53, 144.71, 164.82, 167.53.

Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02. Found: C, 66.05; H, 6.21; N, 10.98.

7-Nitro-1-pentyl-4-propyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5k)
Mp 87.2–88.6 °C.

IR (NaCl): 1689, 1655, 1527, 1344 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.95 (t, 6 H, CH_3), 1.25–1.63 (m, 8 H, CH_2), 3.26 (t, J = 7.2 Hz, 2 H, CH_2), 3.39 (t, J = 7.2 Hz, 2 H, CH_2), 4.13 (s, 2 H, H3), 7.43 (d, J = 7.8 Hz, 1 H, H9), 8.51 (d, J = 7.8 Hz, 1 H, H8), 8.90 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.12, 13.98, 20.12, 22.42, 27.25, 28.87, 42.93, 48.92, 49.88, 122.44, 126.45, 127.17, 130.94, 144.48, 144.49, 164.87, 167.76.

Anal. Calcd for $C_{17}H_{23}N_3O_4$: C, 61.25; H, 6.95; N, 12.60, found: C 61.12; H, 7.01; N, 12.63.

4-Butyl-7-nitro-1-pentyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5l)
Mp 94.1–95.2 °C.

IR (NaCl): 1689, 1654, 1526, 1345 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.92 (t, 6 H, CH_3), 1.26–1.61 (m, 10 H, CH_2), 3.25 (t, J = 7.2 Hz, 2 H, CH_2), 3.38 (t, J = 7.2 Hz, 2 H, CH_2), 4.14 (s, 2 H, H3), 7.44 (d, J = 7.8 Hz, 1 H, H9), 8.53 (d, J = 7.8 Hz, 1 H, H8), 8.91 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.57, 13.92, 20.15, 22.34, 27.13, 29.38, 29.66, 43.87, 46.90, 49.99, 122.43, 126.44, 127.15, 130.92, 144.48, 144.49, 164.87, 167.74.

Anal. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.23; H, 7.25; N, 12.10. Found: C, 62.15; H, 7.29; N, 12.14.

7-Nitro-1,4-dipentyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5m)
Mp 104.2–105.1 °C.

IR (NaCl): 1693, 1654, 1529, 1325 cm^{-1}.

^{1}H NMR(600 MHz, $CDCl_3$): δ = 0.96 (t, 6 H, CH_3), 1.25–1.60 (m, 12 H, CH_2), 3.33 (t, J = 7.2 Hz, 2 H, CH_2), 3.56 (t, J = 7.2 Hz, 2 H, CH_2), 4.16 (s, 2 H, H3), 7.41 (d, J = 7.8 Hz, 1 H, H9), 8.34 (d, J = 7.8 Hz, 1 H, H8), 8.77 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.58, 13.73, 22.15, 22.41, 27.14, 27.25, 29.31, 29.46, 40.74, 46.94, 49.88, 122.41, 126.42, 127.11, 130.94, 144.44, 144.48, 164.84, 167.71.

Anal. Calcd for $C_{19}H_{27}N_3O_4$: C, 63.14; H, 7.53; N, 11.63. Found: C, 63.07; H, 7.58; N, 11.58.

4-Hexyl-7-nitro-1-pentyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5n)
Mp 111.1–112.6 °C.

IR (NaCl): 1690, 1655, 1525, 1345 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.96 (t, 6 H, CH_3), 1.25–1.61 (m, 14 H, CH_2), 3.78 (t, J = 7.2 Hz, 2 H, CH_2), 3.96 (t, J = 7.2 Hz, 2 H, CH_2), 4.14 (s, 2 H, H3), 7.42 (d, J = 7.8 Hz, 1 H, H9), 8.35 (d, J = 7.8 Hz, 1 H, H8), 8.77 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.53, 13.71, 22.18, 22.51, 27.04, 27.15, 27.17, 29.31, 31.71, 31.56, 46.89, 49.48, 122.42, 126.43, 127.14, 130.95, 144.14, 144.42, 164.85, 167.72.

Anal. Calcd for $C_{20}H_{29}N_3O_4$: C, 63.98; H, 7.79; N, 11.19. Found: C, 63.85; H, 7.82; N, 11.22.

7-Nitro-1-pentyl-4-phenethyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5o)
IR (NaCl): 1690, 1654, 1535, 1345 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.90 (t, 3 H, CH_3), 1.20–1.60 (m, 6 H, CH_2), 3.01 (t, J = 7.2 Hz, 2 H, CH_2), 3.65 (t, J = 7.2 Hz, 2 H, CH_2), 3.90 (t, J = 7.2 Hz, 2 H, CH_2), 4.22 (s, 2 H, H3), 7.20–7.38 (m, 5 H), 7.39 (d, J = 7.8 Hz, 1 H, H9), 8.32 (d, J = 7.8 Hz, 1 H, H8), 8.73 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.13, 22.31, 27.62, 28.93, 34.21, 47.42, 50.83, 52.21, 126.73, 126.91, 127.32, 128.25, 128.35, 128.56, 128.67, 128.93, 129.01, 130.92, 144.03, 144.71, 165.12, 167.73.

Anal. Calcd for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.63. Found: C, 66.79; H, 6.42; N, 10.65.

1-Hexyl-7-nitro-4-propyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5p)
Mp 100.5–102.5 °C.

IR (NaCl): 1689, 1651, 1527, 1343 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.90 (t, 6 H, CH_3), 1.20–1.63 (m, 10 H, CH_2), 3.24 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.37 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.15 (s, 2 H, H3), 7.46 (d, *J* = 7.8 Hz, 1 H, H9), 8.57 (d, *J* = 7.8 Hz, 1 H, H8), 8.91 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.6, 13.66, 20.14, 22.46, 26.54, 27.58, 31.86, 40.92, 48.93, 49.77, 122.36, 126.43, 127.24, 130.92, 144.43, 144.57, 164.82, 167.74.

Anal. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.23; H, 7.25; N, 12.10. Found: C, 62.18; H, 7.29; N, 11.07.

4-Butyl-1-hexyl-7-nitro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5q)
Mp 92.5–94.1 °C.

IR (NaCl): 1688, 1653, 1527, 1343 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.90 (t, 6 H, CH_3), 1.09–1.61 (m, 12 H, CH_2), 3.35 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.66 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.14 (s, 2 H, H3), 7.47 (d, *J* = 7.8 Hz, 1 H, H9), 8.34 (d, *J* = 7.8 Hz, 1 H, H8), 8.90 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.57, 13.96, 20.11, 22.62, 26.44, 27.35, 28.86, 31.55, 39.35, 46.39, 48.88, 122.42, 126.44, 127.16, 130.94, 144.48, 144.55, 164.76, 167.76.

Anal. Calcd for $C_{19}H_{27}N_3O_4$: C, 63.14; H, 7.53; N, 11.63. Found: C, 63.05; H, 7.60; N, 11.59.

1-Hexyl-7-nitro-4-pentyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5r)
Mp 94.5–96.2 °C.

IR (NaCl): 1687, 1653, 1527, 1335 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.94 (t, 6 H, CH_3), 1.26–1.66 (m, 14 H, CH_2), 3.23 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.37 (t, *J* = 7.8 Hz, 2 H, CH_2), 4.15 (s, 2 H, H3), 7.48 (d, *J* = 7.8 Hz, 1 H, H9), 8.60 (d, *J* = 7.8 Hz, 1 H, H8), 8.90 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.57, 13.76, 22.48, 22.62, 26.54, 27.10, 27.34, 29.34, 31.52, 40.86, 46.68, 49.78, 122.42, 126.47, 127.15, 130.91, 144.17, 144.43, 164.88, 167.74.

Anal. Calcd for $C_{20}H_{29}N_3O_4$: C, 63.98; H, 7.79; N, 11.19. Found: C, 63.86; H, 7.82; N, 11.15.

1,4-Dihexyl-7-nitro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5s)
Mp 90.5–91.8 °C.

IR (NaCl): 1688, 1654, 1526, 1344 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.92 (t, 6 H, CH_3), 1.28–1.61 (m, 16 H, CH_2), 3.23 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.38 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.14 (s, 2 H, H3), 7.47 (d, *J* = 7.8 Hz, 1 H, H9), 8.59 (d, *J* = 7.8 Hz, 1 H, H8), 8.89 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.55, 13.71, 22.63, 22.72, 26.56, 26.71, 27.17, 27.44, 31.43, 31.62, 40.89, 46.56, 49.72, 122.40, 126.43, 127.13, 130.90, 144.37, 144.51, 164.84, 167.71.

Anal. Calcd for $C_{21}H_{31}N_3O_4$: C, 64.76; H, 8.02; N, 10.79. Found: C, 64.82; H, 7.95; N, 10.75.

1-Hexyl-7-nitro-4-phenethyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5t)
IR (NaCl): 1686, 1654, 1527, 1343 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.90 (t, 3 H, CH_3), 1.29–1.42 (m, 8 H, CH_2), 2.98 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.66 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.87 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.22 (s, 2 H, H3), 7.22–7.38 (m, 5 H), 7.40 (d, *J* = 7.8 Hz, 1 H, H9), 8.33 (d, *J* = 7.8 Hz, 1 H, H8), 8.74 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.11, 22.82, 26.80, 27.50, 31.61, 32.82, 39.81, 48.02, 49.81, 122.32, 123.32, 126.30, 127.21, 128.02, 128.39, 128.70, 128.71, 128.83, 139.52, 143.82, 144.80, 161.31, 166.52.

Anal. Calcd for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.65; N, 10.26. Found: C, 67.42; H, 6.67; N, 10.25.

7-Nitro-1-phenethyl-4-propyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5u)
Mp 42.6–43.4 °C.

IR (NaCl): 1688, 1649, 1525, 1341 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.93 (t, 3 H, CH_3), 1.63 (t, *J* = 7.2 Hz, 2 H, CH_2), 2.88 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.52 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.84 (t, *J* = 7.8 Hz, 2 H, CH_2), 4.58 s, 2 H, H3), 7.07–7.33 (m, 5 H), 7.35 (d, *J* = 7.8 Hz, 1 H, H9), 8.31 (d, *J* = 7.8 Hz, 1 H, H8), 8.75 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.51, 20.32, 33.10, 48.91, 49.82, 52.21, 122.31, 123.30, 126.31, 126.52, 127.80, 128.22, 128.35, 128.56, 128.81, 139.52, 143.82, 144.80, 161.31, 166.12.

Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.45; H, 5.80; N, 11.42.

4-Butyl-7-nitro-1-phenethyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5v)
IR (NaCl): 1689, 1651, 1526, 1342 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.96 (t, 3 H, CH_3), 1.33 (m, 2 H, CH_2), 1.59 (m, 2 H, CH_2), 2.88 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.56 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.89 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.32 (s, 2 H, H3), 7.10–7.33 (m, 5 H), 7.34 (d, *J* = 7.8 Hz, 1 H, H9), 8.31 (d, *J* = 7.8 Hz, 1 H, H8), 8.75 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.80, 20.21, 29.42, 33.10, 46.41, 49.82, 50.20, 122.31, 126.22, 126.30, 127.21, 128.56, 128.78, 129.02, 129.52, 129.71, 139.50, 143.82, 144.81, 161.30, 166.42.

Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02. Found: C, 66.08; H, 6.14; N, 10.95.

7-Nitro-4-pentyl-1-phenethyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5w)
IR (NaCl): 1689, 1650, 1528, 1342 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.90 (t, 3 H, CH_3), 1.14–1.60 (m, 6 H, CH_2), 2.88 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.55 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.75 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.03 (s, 2 H, H3), 7.06–7.34 (m, 5 H), 7.41 (d, *J* = 7.8 Hz, 1 H, H9), 8.30 (d, *J* = 7.8 Hz, 1 H, H8), 8.75 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.12, 22.50, 26.90, 29.33, 33.12, 46.72, 49.81, 50.22, 122.32, 126.31, 127.31, 127.52, 128.58, 128.73, 129.02, 129.51, 129.92, 139.53, 143.82, 144.81, 161.50, 167.40.

Anal. Calcd for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.63. Found: C, 66.75; H, 6.45; N, 10.66.

4-Hexyl-7-nitro-1-phenethyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5x)
IR (NaCl): 1689, 1654, 1526, 1345 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.96 (t, 3 H, CH_3), 1.29–1.60 (m, 8 H, CH_2), 2.70 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.20 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.71 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.14 (s, 2 H, H3), 7.08–7.21 (m, 5 H), 7.54 (d, *J* = 7.8 Hz, 1 H, H9), 8.49 (d, *J* = 7.8 Hz, 1 H, H8), 8.93 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.11, 22.81, 26.82, 31.60, 33.10, 46.71, 49.82, 50.21, 122.32, 125.3, 126.32, 127.21, 127.52, 128.58, 128.73, 129.02, 129.51, 129.92, 139.51, 143.81, 144.81, 161.30, 166.40.

Anal. Calcd for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.65; N, 10.26. Found: C, 67.52; H, 6.67; N, 10.28.

7-Nitro-1,4-bis(phenethyl)-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (5y)

IR (NaCl): 1689, 1654, 1526, 1345 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.70 (t, 2 H, CH_2), 2.85 (t, 2 H, CH_2), 3.53 (t, 2 H, CH_2), 3.74 (t, 2 H, CH_2), 4.21 (s, 2 H, H3), 7.04–7.21 (m, 10 H), 7.54 (d, *J* = 7.8 Hz, 1 H, H9), 8.49 (d, *J* = 7.8 Hz, 1 H, H8), 8.93 (s, 1 H, H6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 32.82, 33.12, 48.01, 49.80, 50.21, 122.32, 123.52, 126.32, 126.71, 126.80, 127.20, 127.31, 127.58, 127.73, 128.02, 128.41, 128.62, 128.73, 128.86, 139.51, 139.59, 143.82, 144.81, 161.31, 167.41

Anal. Calcd for $C_{25}H_{23}N_3O_4$: C, 69.92; H, 5.40; N, 9.78. Found: C, 69.98; H, 5.42; N, 9.82.

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