# New Synthetic Methodology for Construction of the 1,3,4,5-Tetrahydro-2*H*-1,3-benzodiazepin-2-one Skeleton

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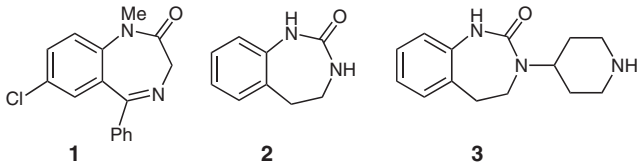
**Abstract:** We hereby report a new synthetic methodology for construction of the 1,3,4,5-tetrahydro-2*H*-1,3-benzodiazepin-2-one skeleton. 2-(2-Carboxyethyl)benzoic acid was converted into the corresponding bis(acyl azide). Curtius rearrangement of the diazide followed by reaction with alcohols provided diurethane derivatives. Ring-closure reaction of the diurethanes with base resulted in formation of the 1,3-benzodiazepin-2-one skeleton.

**Key words:** acyl azide, isocyanate, Curtius rearrangement, urethanes, benzodiazepinone

Since the initial discovery of the sedative and tranquilizing effects of diazepam (**1**) (Figure 1), benzodiazepines have been extensively investigated.[1] Further extensive investigations of this class of seven-membered *N*-heterocycles have also led to the development of a number of pharmacologically active agents directed against other diseases such as cancer, HIV and cardiac arrhythmia.[2] Relatively little work, however, has been done on the synthesis of the 1,3-benzodiazepin-2-one **2**. Some derivatives of **2**, such as **3** substituted at the nitrogen atom with a piperidine ring or other substituents, are CGRP (calcitonin gene-related peptide) receptor antagonists for the treatment of migraine.[3] Therefore, a great attention has been directed towards the synthesis of **3** and its derivatives in recent years.




1 2 3

**Figure 1**

The most general synthetic approach to 1,3-benzodiazepin-2-one **2** yet reported involves the reaction of *o*-aminoalkyl-substituted aromatic amines and selenium in the presence of *N*-methylpyrrolidone.[4] More recently, Han and co-workers[5] succeeded in the synthesis of **3** and its derivatives by Stille reaction of *o*-halonitrobenzenes followed by Michael addition of *tert*-butyl 4-aminopiperidine-1-carboxylate to the resulting activated vinyl compound, hydrogenation and cyclic urea formation.

By targeting the synthesis of nitrogen-containing compounds of biological interest with parent skeleton **2**, we wish to report here a novel route for formation of the 1,3-benzodiazepin-2-one skeleton **2** based upon the double Curtius rearrangement of the diazide derived from 2-(2-carboxyethyl)benzoic acid (bishomophthalic acid, **6**) followed by cyclization.

2-(2-Carboxyethyl)benzoic acid (**6**) can serve as a building block for 1,3-benzodiazepin-2-one **2**. The starting material **6** has been synthesized starting from β-naphthol (Scheme 1). β-Naphthol (**4**) was first oxidized to *o*-carboxycinnamic acid (**5**) by reaction with peroxyacetic acid. Diacid **5** was then reacted with Raney nickel in basic aqueous solution to give the desired acid **6**, as described in the literature.[6]

For the synthesis of bis(acyl azide) **8**, 2-(2-carboxyethyl)benzoic acid (**6**) was treated with oxalyl chloride in the presence of *N*,*N*-dimethylformamide in dichloromethane, followed by addition of a solution of sodium azide in a mixture of acetone and water (Scheme 1).

After the successful synthesis of bis(acyl azide) **8**, we turned our attention to the Curtius rearrangement. Our plan for the construction of the desired heterocyclic ring system involved an intramolecular cyclization reaction of the diisocyanate **9**, which can be generated by the Curtius reaction.[7] Thus, bis(acyl azide) **8** was allowed to reflux in benzene for one hour to effect the transformation of the acyl azide functionalities to the corresponding isocyanate groups (Scheme 2). Treatment of the resulting diisocyanate **9** with aniline in dichloromethane at room temperature for 12 hours gave the expected diurea **10** in 69% yield.

As a result of this, we redirected our efforts to the ring-closure reaction of **10**, already bearing the necessary functionalities, as shown in Scheme 2. All efforts with various bases, such as pyridine, potassium carbonate and cesium carbonate, did not reveal the formation of the ring-closure product **11**; however, treatment of diurea **10** with lithium diisopropylamide under reflux for one week afforded *N*,*N*′-diphenylurea[8] (**12**) as the isolable product in 47% yield (based on the consumed starting material). The spectroscopic data of **12** was in complete agreement with those

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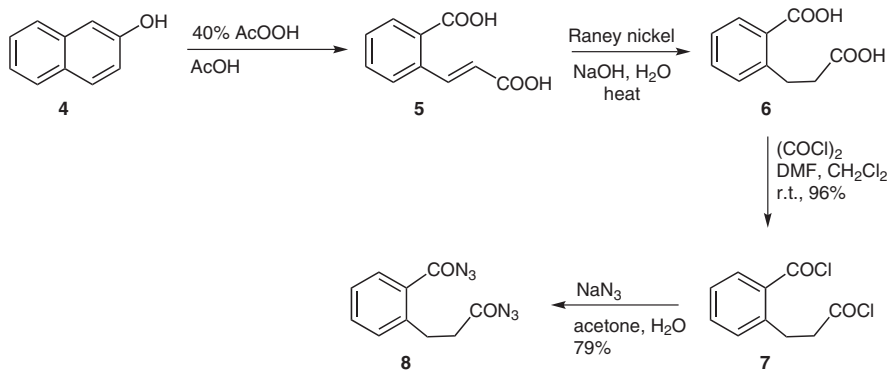
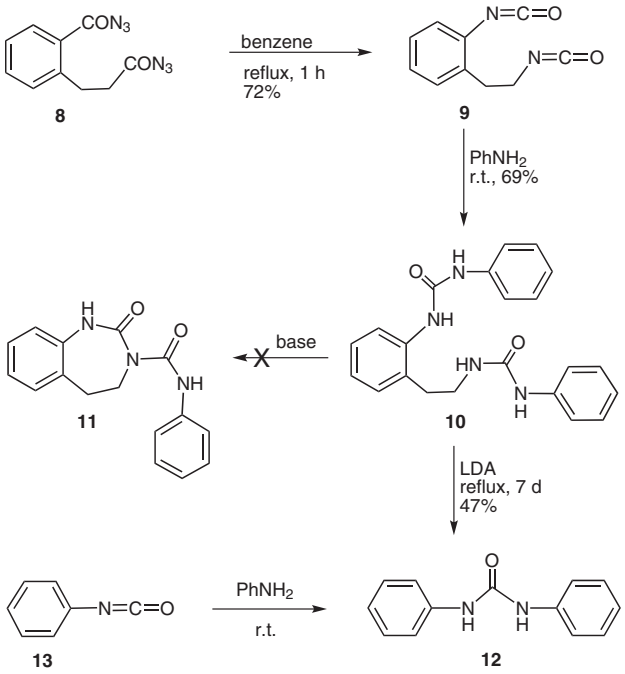



**Scheme 1** Synthesis of the key compound, bis(acyl azide) **8**



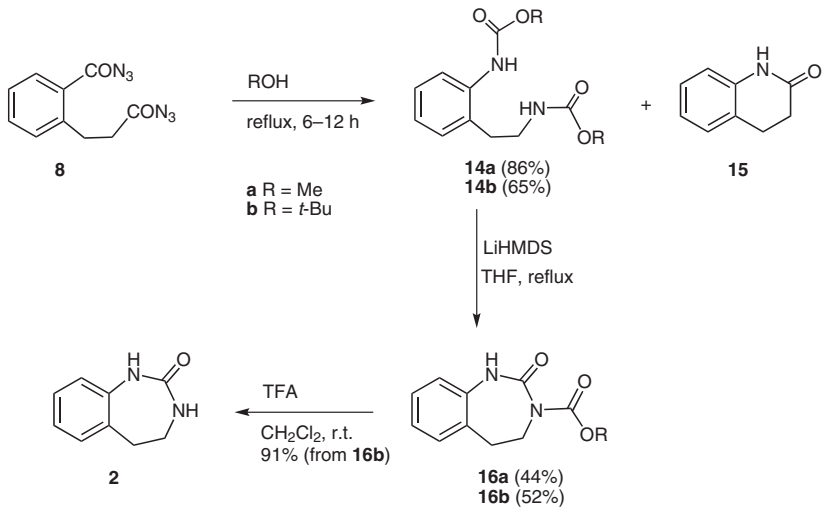

**Scheme 2** Synthesis of diurea **10** and its reaction with lithium diisopropylamide

of **12** obtained by the reaction of phenyl isocyanate (**13**) with aniline (Scheme 2).

After the failure of the ring-closure reaction of **10**, we decided to increase the reactivity of the carbonyl groups in **10**. For that purpose, bis(acyl azide) **8** was reacted with methanol and *tert*-butyl alcohol at the reflux temperature of the alcohol to give the corresponding diurethane derivatives **14a** and **14b**, respectively. Reaction of **14a** and **14b** with various bases, such as sodium hydride, potassium carbonate and triethylamine, did not result in the formation of any trace of the ring-closure products; however, when **14a** and **14b** were reacted with lithium hexamethyldisilazide for 30–60 minutes, the 1,3-benzodiazepinone derivatives **16a** and **16b** were obtained in 44% and 52% yield, respectively. Prolonged reaction time resulted in a decreased amount of the desired product.

Spectroscopic data allowed the assignment of the structures **16a** and **16b**. In order to confirm the structure and elucidate the structural impact of the substituents on the benzodiazepinone scaffold, we conducted single crystal X-ray analysis studies on the product **16a** (Figure 2).

The compound crystallizes in the triclinic space group $P\bar{1}$, with two molecules in the unit cell (Figure 3). The diazepinone ring adopts a slightly distorted boat conformation.




**Scheme 3** Synthesis of diurethanes **14a** and **14b**, and their ring-closure reactions

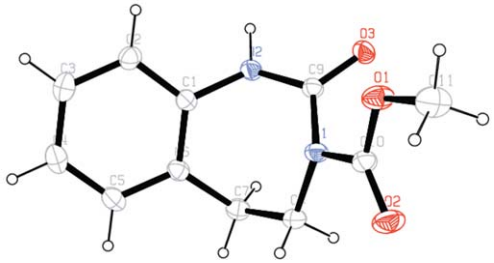


**Figure 2** Single crystal X-ray diffraction analysis of **16a**; the ORTEP drawing depicts thermal ellipsoids at a 40% probability level

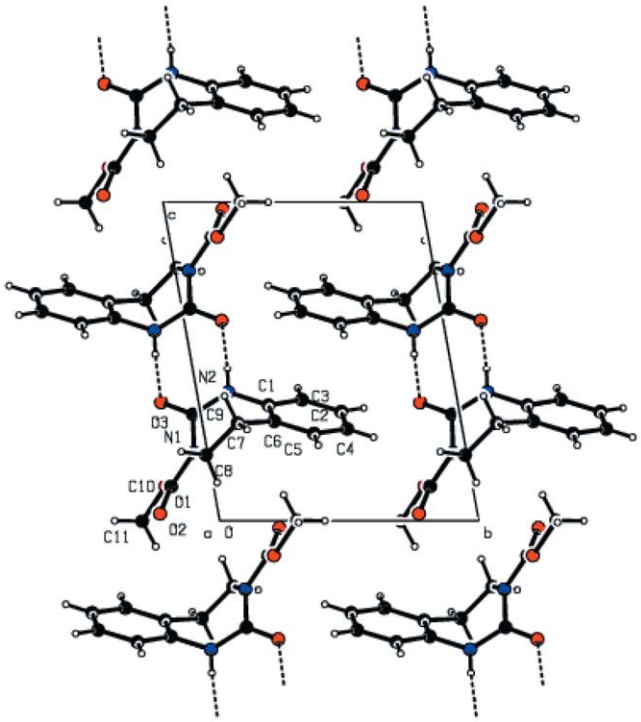
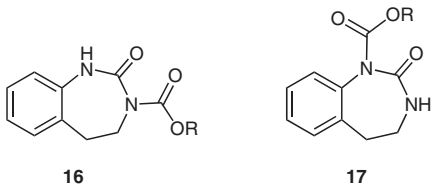


**Figure 3** Unit cell along the *a*-axis (data for **16a**); dashed lines indicate intermolecular hydrogen bonding

The unsymmetrical distortion arises from the torsional strains between the substituted units. The C=O bond lengths are within the expected range [1.201(4)–1.225(4) Å]. Furthermore, the compound exists as a dimer, exhibiting intermolecular N–H···O hydrogen bonding [N2–H···O3$^{i}$ = 2.899(2) Å; N2–H···O3$^{i}$ = 175°; symmetry code (i); 1-x,-y,1-z].

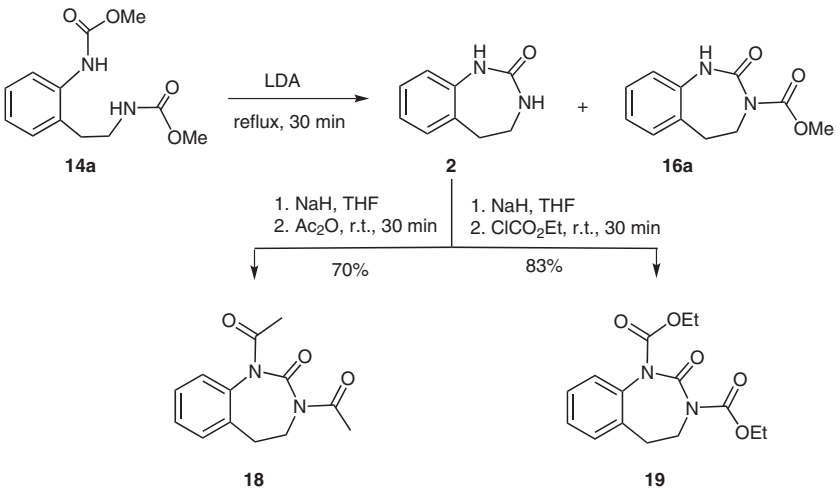
In the reaction of diurethane **14a** or **14b** with base, a mixture of two regioisomers **16** and **17** is expected as a result of the attack of the amide functionalities to the two carbonyl groups (Figure 4). Because of the increased acidity of the NH attached directly to the benzene ring, one would expect **17** as the sole or major product. Surprisingly, the isomers **16a** and **16b** were formed as sole products. We assume that the abstraction of the more acidic NH proton in **14** is hindered by the bulky base which is used, or the nucleophilicity of the amide functionality conjugated with the benzene ring may also be reduced due to the conjugation.



**16** **17**

**Figure 4**

Hydrolysis of the half ester **16b** with trifluoroacetic acid in dichloromethane at room temperature gave the 1,3-benzodiazepin-2-one **2** in high yield (Scheme 3). The spectroscopic data of **2** was fully in accordance with the proposed structure.[4] Furthermore, we reacted diurethane **14a** with lithium diisopropylamide in tetrahydrofuran; two products were formed and, after chromatographic separation, were identified as the cyclization products **2** and **16a** (Scheme 4). For further derivatization of 1,3-benzodiazepin-2-one **2**, reaction with sodium hydride in tetrahydrofuran followed by quenching with acetic anhydride




**14a** **2** **16a** **18** **19**

**Scheme 4** Reaction of diurethane **14a** with lithium diisopropylamide, and derivatization of **2**

provided the diacetyl derivative **18**. Similarly, the diester derivative **19** was obtained by reaction of the initially formed salt with ethyl chloroformate.

In summary, the present investigation has resulted in the preparation of 1,3,4,5-tetrahydro-2*H*-1,3-benzodiazepin-2-one (**2**) and its derivatives by application of a new synthetic methodology, where two Curtius rearrangements are involved as the key step. This methodology should be a suitable synthetic method for the introduction of further substituents at the aromatic ring, as well as the seven-membered ring. Further research in this field is in progress.

Melting points were determined on a Thomas Hoover capillary melting point apparatus. IR spectra were recorded on a Perkin Elmer 980 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance instrument at 400 and 100 MHz, respectively. Apparent splitting is given in all cases. Mass spectra were recorded on an Agilent Technologies 5975C mass spectrometer operating at an ionization potential of 70 eV. Column chromatography was performed on Merck silica gel (60 mesh). TLC was carried out on Merck 0.2 mm silica gel 60 $F_{254}$ analytical aluminum plates.

**1-Chloro-3-[2-(chlorocarbonyl)phenyl]propan-1-one (7)**

To a suspension of 2-(2-carboxyethyl)benzoic acid (**6**; 1.0 g, 5.15 mmol) in $CH_2Cl_2$ (50 mL), oxalyl chloride (1.77 mL, 20.6 mmol) was added quickly at r.t. This was followed by the addition of DMF (2 drops) as catalyst, and the reaction mixture was stirred for 4 h at r.t. The reaction was completed after all the starting material had dissolved in the $CH_2Cl_2$. The reaction mixture was concentrated under reduced pressure to afford dichloride **7** as a colorless oil; yield: 1.14 g (96%).

IR (KBr): 2922 (w), 1797 (s), 1771 (s), 1451 (w), 1275 (m), 1188 (s), 750 (s) cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.0 Hz, H-6′), 7.59 (t, *J* = 7.2 Hz, H-5′), 7.43 (t, *J* = 7.7 Hz, H-4′), 7.37 (d, *J* = 7.7 Hz, H-3′), 3.27–3.19 (m, 4 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 172.8, 168.1, 141.4, 134.9, 134.5, 132.2, 131.7, 127.8, 47.5, 30.0.

**1-Azido-3-[2-(azidocarbonyl)phenyl]propan-1-one (8)**

To a soln of dichloride **7** (1.14 g, 4.93 mmol) in acetone (10 mL) at 0 °C, a soln of $NaN_3$ (1.28 g, 19.7 mmol) in $H_2O$ (5 mL) was added. Precipitation of inorganic salt was immediately observed. After completion of the addition, the resulting mixture was stirred for 1 h and $H_2O$ (25 mL) was added. The mixture was extracted with EtOAc (3 × 75 mL). The organic extracts were dried ($MgSO_4$). After removal of the solvent under reduced pressure, bis(acyl azide) **8** was obtained as a colorless oil which was directly used for the next step without further purification; yield: 0.948 g (79%).

IR (KBr): 2979 (w), 2275 (s), 2137 (s), 1715 (s), 1692 (s), 1229 (s), 1082 (m), 913 (m), 748 (s) cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.88 (dd, *J* = 7.8, 1.2 Hz, H-6′), 7.43 (dt, *J* = 7.5, 1.4 Hz, H-4′), 7.25–7.21 (m, 2 H, H-3′ and H-5′), 3.23 (t, *J* = 7.6 Hz, 2 H, H-2), 2.63 (t, *J* = 7.6 Hz, 2 H, H-1).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 180.3, 173.7, 143.5, 134.4, 132.3, 132.0, 129.6, 127.5, 38.5, 30.2.

**1-Isocyanato-2-(2-isocyanatoethyl)benzene (9)**

Bis(acyl azide) **8** (0.59 g, 2.4 mmol) was dissolved in anhyd benzene (50 mL) and the mixture was refluxed for 1 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to give the diisocyanate **9** as a colorless oil which was directly used for the next step without further purification; yield: 0.33 g (72%).

IR (KBr): 2968 (w), 2274 (s), 2146 (m), 1713 (m), 1513 (m), 1226 (m), 756 (m) cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.13 (m, 2 H, H-4 and H-5), 7.10 (br dd, *J* = 7.3, 1.4 Hz, H-3 or H-6), 7.06 (br dd, *J* = 7.9, 1.2 Hz, H-3 or H-6), 3.46 (t, *J* = 6.8 Hz, 2 H, H-2′), 2.87 (t, *J* = 6.8 Hz, 2 H, H-1′).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 134.4, 133.7, 132.6, 130.3, 128.3, 128.0, 127.3, 124.3, 44.7, 35.8.

***N*-(2-{2-[(Anilinocarbonyl)amino]ethyl}phenyl)-*N*′-phenylurea (10)**

A soln of $PhNH_2$ (1.2 g, 12.9 mmol) in benzene (5 mL) was added dropwise to a stirred soln of diisocyanate **9** (1.0 g, 5.32 mmol) in anhyd $CH_2Cl_2$ (50 mL) at r.t. and the mixture was stirred for 12 h. The formed diurea **10** was collected by filtration and washed with $CH_2Cl_2$ (5–10 mL) to give a colorless powder; yield: 1.36 g (69%); mp 207–208.5 °C.

IR (KBr): 3347 (s), 3218 (m), 3043 (m), 1648 (s), 1620 (s), 1565 (s), 1317 (s), 1179 (s), 893 (w), 709 (s), 691 (s) cm$^{-1}$.

$^1$H NMR (400 MHz, acetone-$d_6$): δ = 8.84 (s, NH), 8.63 (s, NH), 8.33 (s, NH), 7.87 (dd, *J* = 7.5, 1.2 Hz, 1 H), 7.46 (br d, *J* = 7.6 Hz, 2 H), 7.40 (br d, *J* = 7.6 Hz, 2 H), 7.28 (br t, *J* = 7.6 Hz, 2 H), 7.23 (br t, *J* = 7.5 Hz, 2 H), 7.21–7.18 (m, 2 H), 7.01 (dt, *J* = 7.4, 1.1 Hz, 1 H), 6.98 (br t, *J* = 7.4 Hz, 1 H), 6.92 (br t, *J* = 7.3 Hz, 1 H), 6.35 (t, *J* = 5.6 Hz, NH), 3.38–3.26 (m, 2 H), 2.79 (t, *J* = 8.0 Hz, 2 H).

$^{13}$C NMR (100 MHz, acetone-$d_6$): δ = 155.8, 152.8, 140.2, 139.8, 137.4, 129.5, 129.2, 128.8, 128.6, 126.7, 122.9, 121.74, 121.69, 121.3, 118.1, 117.9, 39.1, 31.7.

Anal. Calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.22; H, 5.88; N, 15.03.

***N*,*N*′-Diphenylurea (12); Reaction of Diurea 10 with Lithium Diisopropylamide**

LDA soln was prepared by the addition of 1.6 M *n*-BuLi in hexane (3.67 mL, 5.9 mmol) to a soln of freshly distilled *i*-$Pr_2NH$ (0.83 mL, 5.9 mmol) in THF (5 mL) at –78 °C, followed by stirring for 30 min. Diurea **10** (0.5 g, 1.34 mmol) was added to the solution. The mixture was refluxed for 7 d. The reaction was monitored by TLC. After completion of the reaction, aq $NH_4Cl$ soln (20 mL) was added, the mixture was extracted with EtOAc (3 × 50 mL) and the extracts were dried ($MgSO_4$). Removal of EtOAc gave a mixture (0.35 g). Chromatography of this mixture over silica gel (EtOAc–hexane, 1:2) gave *N*,*N*′-diphenylurea[8] (**12**); yield: 99 mg (35%; 47% based on the consumed starting material); as the second fraction, unreacted starting material **10** was isolated (130 mg, 0.35 mmol).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.72 (s, 2 H, NH), 7.50 (br d, *J* = 7.6 Hz, 4 H), 7.32 (br t, *J* = 7.6 Hz, 4 H), 7.00 (br t, *J* = 7.6 Hz, 2 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 152.5, 139.7, 128.7, 121.8, 118.2.

**Methyl2-{2-[(Methoxycarbonyl)amino]ethyl}phenylcarbamate (14a)**

Bis(acyl azide) **8** (2.87 g, 11.75 mmol) was dissolved in MeOH (150 mL) and the mixture was refluxed for 6 h. The reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. Chromatography of the residue on silica gel (50 g; EtOAc–$CH_2Cl_2$, 1:3) afforded the known 3,4-dihydroquinolin-2(1*H*)-one[9] (**15**) as the first fraction; yield: 0.092 g (5.4%). The second fraction was identified as diurethane **14a**; yield: 2.55 g (86%); colorless crystals (EtOAc); mp 82–84 °C.

IR (KBr): 3324 (s), 3015 (m), 2953 (m), 1704 (s), 1533 (s), 1242 (s), 1068 (s), 757 (s) $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.79 (br s, 1 H), 7.42 (br s, 1 H, NH), 7.18 (t, *J* = 7.7 Hz, 1 H), 7.06 (d, *J* = 7.3 Hz, 1 H), 6.99 (t, *J* = 7.3 Hz, 1 H), 4.98 (br s, 1 H, NH), 3.72 (s, 3 H, $OCH_3$), 3.64 (s, 3 H, $OCH_3$), 3.23 (dt, *J* = 7.4, 6.2 Hz, 2 H, H-2′), 2.75 (t, *J* = 7.2 Hz, 2 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 157.8, 155.1, 136.1, 129.9, 129.2, 127.6, 124.5, 122.6, 52.5, 52.3, 41.3, 31.8.

Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.43; H, 6.43; N, 11.12.

### *tert*-Butyl 2-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}phenylcarbamate (14b)

Bis(acyl azide) **8** (2.37 g, 9.7 mmol) was dissolved in *t*-BuOH (200 mL) and the mixture was refluxed for 12 h. The reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. Chromatography of the residue on silica gel (50 g; EtOAc–*n*-hexane, 1:3) afforded diurethane **14b**; yield: 2.12 g (65%); colorless crystals (EtOH–*n*-hexane); mp 90–92 °C.

IR (KBr): 3333 (s), 2979 (m), 2934 (m), 1690 (s), 1520 (s), 1166 (s), 744 (s) $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.78 (br d, *J* = 7.4 Hz, 1 H, H-6), 7.43 (br s, 1 H, NH), 7.14 (dt, *J* = 7.2, 1.6 Hz, 1 H, H-5), 7.01 (br d, *J* = 6.7 Hz, 1 H, H-3), 6.93 (br t, *J* = 7.3 Hz, 1 H, H-4), 4.80 (br s, 1 H, NH), 3.16 (dt, *J* = 7.8, 6.5 Hz, 2 H, H-2′), 2.70 (t, *J* = 7.8 Hz, 2 H), 1.45 [s, 9 H, $OC(CH_3)_3$], 1.39 [s, 9 H, $OC(CH_3)_3$].

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 156.7, 153.8, 136.8, 129.7, 128.7, 127.4, 123.7, 122.2, 80.0, 79.7, 41.1, 32.1, 28.4, 28.0.

Anal. Calcd for $C_{18}H_{28}N_2O_4$: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.01; H, 8.25; N, 8.62.

### Methyl 2-Oxo-1,2,4,5-tetrahydro-3*H*-1,3-benzodiazepine-3-carboxylate (16a)

Diurethane **14a** (500 mg, 1.98 mmol) was dissolved in THF (25 mL) under $N_2$ atmosphere and reacted with LiHMDS as described for the reaction of **14b** below. After reaction workup, the residue was chromatographed on silica gel (EtOAc–$CH_2Cl_2$, 1:1) to give **16a** as colorless crystals (EtOAc–*n*-hexane); yield: 176 mg (44%); mp 145–147 °C. Prolonged reaction time resulted in decreased yield of the product; the hydrolysis product was formed.

IR (KBr): 3245 (m), 2956 (w), 2916 (w), 1700 (s), 1403 (m), 1309 (m), 1219 (m), 772 (s) $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.21 (br s, 1 H, NH), 7.15–7.11 (m, 2 H), 7.02 (dt, *J* = 7.4, 1.3 Hz, 1 H, H-7), 6.82 (br dd, *J* = 7.9, 1.4 Hz, 1 H, H-6), 3.95 (t, *J* = 6.1 Hz, 2 H, H-4), 3.73 (s, 3 H, $OCH_3$), 3.03 (t, *J* = 6.1 Hz, 2 H, H-5).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 155.5, 154.4, 135.8, 130.7, 128.6, 127.6, 124.9, 121.2, 53.8, 46.5, 31.6.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.62; H, 5.49; N, 12.70.

### *tert*-Butyl 2-Oxo-1,2,4,5-tetrahydro-3*H*-1,3-benzodiazepine-3-carboxylate (16b)

Diurethane **14b** (1.14 g, 3.4 mmol) was dissolved in THF (25 mL) under $N_2$ atmosphere. A soln of 1 M LiHMDS in THF (5.1 mL, 5.1 mmol) was added dropwise and the resulting mixture was refluxed for 1 h. After completion of the reaction, aq $NH_4Cl$ soln (25 mL) was added, the mixture was extracted with EtOAc (3 × 50 mL) and the extracts were dried ($MgSO_4$). After evaporation of the solvent, the residue was crystallized (EtOAc–*n*-hexane) to give **16b** as colorless crystals; yield: 462 mg (52%); mp 177–179 °C.

IR (KBr): 3243 (m), 3162 (m), 3003 (w), 2989 (w), 2901 (w), 1702 (s), 1156 (m), 759 (s) $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.49 (br s, 1 H, NH), 7.19 (br d, *J* = 7.3 Hz, 1 H, H-9), 7.17 (br d, *J* = 7.0 Hz, 1 H, H-6), 7.08–7.03 (m, 2 H, H-7 and H-8), 3.98 (t, *J* = 6.0 Hz, 2 H, H-4), 3.09 (t, *J* = 6.0 Hz, 2 H, H-5), 1.51 [s, 9 H, $OC(CH_3)_3$].

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 156.2, 152.5, 136.4, 130.7, 128.1, 127.3, 124.2, 121.3, 82.4, 45.3, 32.3, 28.1.

Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.89; H, 6.92; N, 10.70.

### 1,3,4,5-Tetrahydro-2*H*-1,3-benzodiazepin-2-one (2)

1,3-Benzodiazepine-3-carboxylate **16b** (80 mg, 0.3 mmol) was dissolved in $CH_2Cl_2$ (10 mL). TFA (235 mg, 2 mmol) was added dropwise at 0 °C and the mixture was stirred for 1 h at r.t. After completion of the reaction, $H_2O$ (20 mL) was added and the resulting mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with $H_2O$ (25 mL) and dried ($MgSO_4$). Removal of the solvent gave the crude product **2** [yield: 45 mg (91%)] which was crystallized (EtOAc–*n*-hexane) to give colorless crystals; mp 170–172 °C (Lit.[4b] 170.5–171 °C, Lit.[4c] 169–171 °C).

$^1H$ NMR (400 MHz, $CD_3OD$): δ = 7.00 (br t, *J* = 7.4 Hz, 1 H, H-8), 6.94 (br d, *J* = 7.5 Hz, 1 H, H-9), 6.85 (br d, *J* = 8.0 Hz, 1 H, H-6), 6.80 (br t, *J* = 7.5 Hz, 1 H, H-7), 4.75 (br s, 2 H, NH), 3.26–3.24 (m, 2 H, H-4), 2.89–2.87 (m, 2 H, H-5).

$^{13}C$ NMR (100 MHz, $CD_3OD$): δ = 159.2, 138.4, 130.5, 130.2, 127.8, 123.0, 119.7, 43.2, 35.3.

### Reaction of Methyl 2-{2-[(Methoxycarbonyl)amino]ethyl}phenylcarbamate (14a) with Lithium Diisopropylamide

LDA soln was prepared by the dropwise addition of 1.6 M *n*-BuLi in hexane (6.25 mL, 10 mmol) to a soln of *i*-$Pr_2NH$ (1.0 g, 9.9 mmol) in THF (5 mL) at –78 °C, followed by stirring for 30 min. Then, diurethane **14a** (1.0 g, 3.96 mmol) in THF (5 mL) was added at –78 °C. The resulting solution was stirred for 30 min at –78 °C and an additional 30 min at the reflux temperature. The resulting reaction mixture was quenched with sat. aq $NH_4Cl$ soln (25 mL), the mixture was extracted with EtOAc (3 × 50 mL) and the extracts were dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (EtOAc–$CH_2Cl_2$, 1:3) which afforded three compounds in the following order: unreacted starting material **14a** (185 mg, 0.73 mmol), **16a** [yield: 105 mg (15% based on the consumed starting material)] and **2** [yield: 225 mg (43% based on the consumed starting material)].

### 1,3-Diacetyl-1,3,4,5-tetrahydro-2*H*-1,3-benzodiazepin-2-one (18)

1,3-Benzodiazepin-2-one **2** (120 mg, 0.74 mmol) was dissolved in THF (10 mL) and the solution was cooled to 0 °C. NaH (60%; 150 mg, 3.75 mmol) was added and the reaction mixture was allowed to warm to r.t. and was stirred for 30 min. Then, $Ac_2O$ (500 mg, 4.9 mmol) was added and the mixture was stirred for an additional 30 min at r.t. After completion of the reaction, excess NaH was quenched by the dropwise addition of $H_2O$. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with $H_2O$ (2 × 25 mL), dried ($MgSO_4$) and the solvent was evaporated to give the crude diacetyl derivative **18**. Chromatography of the residue over a short silica gel column (EtOAc–$CH_2Cl_2$, 1:1) gave pure **18** as a colorless oil; yield: 127 mg (70%).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.24–7.17 (m, 4 H), 4.01 (br s, 2 H, H-4), 3.00 (t, *J* = 6.8 Hz, 2 H, H-5), 2.34 (s, 3 H, $CH_3$), 2.24 (s, 3 H, $CH_3$).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 170.3, 168.5, 154.7, 132.9, 130.8, 128.2, 127.02, 126.97, 125.4, 42.0, 27.8, 23.2, 22.3.

MS: *m*/*z* (%) = 246 (6) [$M^+$], 204 (100) [$MH^+ - COCH_3$], 161 (38) [$MH^+ - 2 \times COCH_3$], 106 (50), 72 (87).

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.02; H, 5.56; N, 11.61.

**Diethyl 2-Oxo-4,5-dihydro-1*H*-1,3-benzodiazepine-1,3(2*H*)-dicarboxylate (19)**

1,3-Benzodiazepin-2-one **2** (120 mg, 0.74 mmol) was carboxylated by adding NaH as described above, then adding ethyl chloroformate (540 mg, 5 mmol). Chromatography of the residue over a short silica gel column (EtOAc–$CH_2Cl_2$, 1:1) gave pure diester derivative **19**; yield: 188 mg (83%); mp 62–64 °C.

IR (KBr): 2984 (w), 1791 (s), 1728 (s), 1370 (m), 1220 (s), 773 (s) $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.15 (m, 4 H), 4.23 (q, *J* = 7.0 Hz, 2 H, $OCH_2$), 4.13 (q, *J* = 7.0 Hz, 2 H, $OCH_2$), 3.97 (t, *J* = 6.5 Hz, 2 H, H-4), 3.03 (t, *J* = 6.5 Hz, 2 H, H-5), 1.23 (t, *J* = 7.0 Hz, 3 H, $CH_3$), 1.18 (t, *J* = 6.5 Hz, 3 H, $CH_3$).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 153.7, 152.9, 152.2, 135.2, 132.5, 129.7, 128.6, 128.5, 127.2, 63.5, 63.4, 46.1, 30.0, 14.23, 14.16.

MS: *m*/*z* (%) = 306 (15) [$M^+$], 234 (12) [$MH^+ - COOEt$], 188 (38), 162 (10), 146 (25), 132 (100), 118 (72), 102 (50), 77 (25).

Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.51; H, 6.12; N, 9.16.

**Single Crystal X-ray Analysis of Compound 16a**

Full crystallographic parameters (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre under reference number CCDC 749741. These data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

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