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Facile synthesis of 1,4-benzodiazepin-3-ones from *o*-bromobenzylamines and amino acids via a cascade coupling/condensation process

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ABSTRACT

CuI-catalyzed coupling of 2-bromobenzylamines and α-amino acids and subsequent condensative cyclization (directly or mediated with DPPA) provides 1,4-benzodiazepin-3-ones in moderate yields. Using L-proline and L-valine as the starting materials enantiopure products are obtained although partial racemization occurs for other amino acids.

1. Introduction

1,4-Benzodiazepin-3-one is an unique core structure for developing bioactive molecules.[1] The known compounds with this skeleton include SB-214857 (Fig. 1) that has been used for treatment of cardiovascular diseases in clinic trials,[1a,b] vasopressin V2 receptor agonist **1**,[1c] and mitochondrial F1F0 ATP hydrolase inhibitor **2**.[1d] In addition, several 1,4-benzoazepin-3-ones[1e–g] such as compound **3** have been employed as β-turn mimetics for drug discovery.

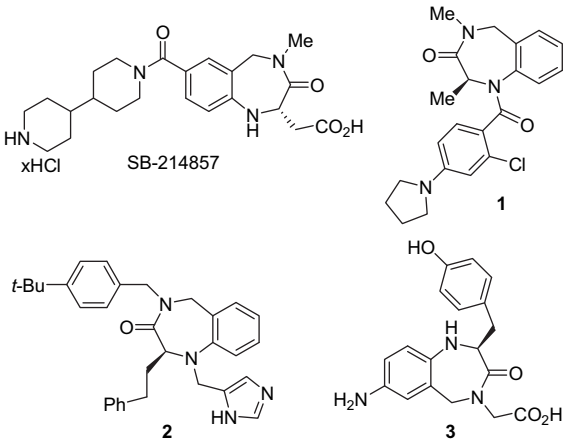

Figure 1. Structures of some 1,4-benzoazepin-3-ones.

For most existing approaches to 1,4-benzoazepin-3-ones, the closure of the hetereocyclic ring is the key step.[1–4] One method is via the intramolecular nucleophilic aromatic substitution.[1a,2] To accelerate the substitution, a carboxyl ester or nitro group is usually placed *para* or *ortho* to the leaving group, which is only suitable for preparing some special 1,4-benzoazepin-3-ones. Another popular method is through the formation of the amide bond, which requires to prepare available precursor through multiple steps reactions.[1h,3]

Recently developed metal-catalyzed N-arylation[5,6] provides an alternative approach to 1,4-benzoazepin-3-ones. Using Pd/bidentate phosphine as a catalyst, Ferraccioli and co-workers achieved seven-membered ring formation through an intramolecular N-arylation.[7] Our group revealed that CuI-catalyzed intramolecular N-arylation of an aspartic acid derivative proceeded smoothly to provide a precursor for assembly of SB-214857.[6b] In this paper, we wish to report a one-pot procedure to 1,4-benzoazepin-3-ones, which relies on an intermolecular N-arylation and subsequent condensative cyclization of *N*-substituted 2-bromobenzyl-amines and amino acids.

2. Results and discussion

2.1. CuI-catalyzed coupling reaction of 2-halobenzylamines with L-proline and subsequent condensative cyclization

As indicated in Table 1, we started our investigations by carrying out a coupling reaction of *N*-benzyl-2-bromo-benzylamine with

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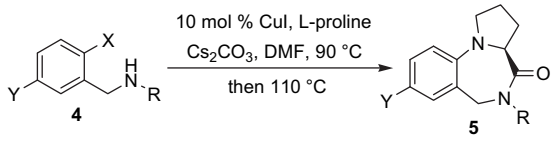
L-proline.[6a] It was found that under the effect of 10 mol % CuI and Cs_2CO_3, this reaction worked in DMF at 90 °C to give the coupling/condensative cyclization product directly. However, the desired product **5a** was isolated in only moderate yield (entry 1). We wondered if the condensative cyclization was a rate-determining step for this process, and therefore decided to improve the yield by increasing reaction temperatures after the coupling step was completed. To our delight, a 64% yield was observed by heating at 110 °C (entry 2).

Table 1
CuI-catalyzed coupling reaction of 2-halobenzyl-amines with L-proline and subsequent condensative cyclization[a]



Entry	X	Y	R	Product	Yield[b] (%)
1[c]	Br	H	Bn	**5a**	47
2	Br	H	Bn	**5a**	64
3	I	H	Bn	**5a**	63
4	Br	NO_2	Bn	**5b**	48
5	Br	OMe	Bn	**5c**	12
6[d]	Br	CO_2Me	Bn	**5d**	55
7	Br	F	Bn	**5e**	65
8[d]	Br	H	allyl	**5f**	60
9[d]	Br	H	*n*-Bu	**5g**	63

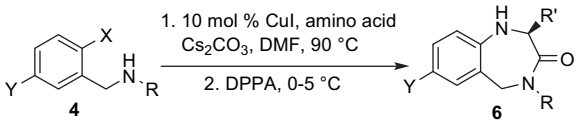
[a] Reaction conditions: 2-halobenzylamine (2 mmol), L-proline (3 mmol), CuI (0.2 mmol), Cs_2CO_3 (2 mmol), DMF (4 mL), 90 °C, 21 h; 110 °C, 24 h.
[b] Isolated yield.
[c] The reaction was conducted at 90 °C for 24 h.
[d] The coupling was conducted at 90 °C for 21 h, then DPPA (3 mmol), 0–5 °C, 8 h.

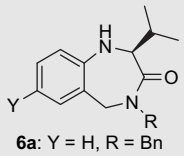
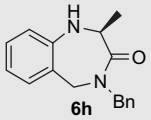
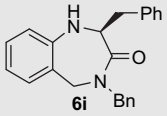
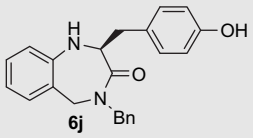
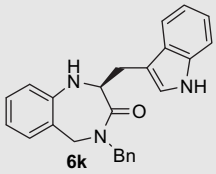
Switching aryl bromide to aryl iodide gave a similar result (entry 3), which led us to utilize aryl bromides as our substrates (aryl chlorides have not be attempted) in the subsequent studies. Other 2-bromobenzylamines with a substituent group on the benzene ring were also compatible with this process, delivering the corresponding tricyclic compounds **5b**–**5e** (entries 4–7). But the electronic-rich substrate provided low yield (entry 5), indicating that the electronic nature at the benzene ring plays an important role for this process. Next, we tried to change *N*-substituents, and found that both allyl and *n*-butyl substituted products were isolated in satisfactory yields (entries 8 and 9). Noteworthy is that similar yields could be observed if the condensative cyclization step was prompted by adding diphenyl phosphoryl azide (DPPA), after coupling of 2-bromobenzylamines and L-proline (entries 6, 8 and 9).

2.2. Elaboration of 1,4-benzoazepin-3-ones via coupling with other amino acids

To further explore the reaction scope, other α-amino acids were tested under the optimized reaction conditions and the results are summarized in Table 2. When L-valine was employed, coupling step worked well. However, no direct condensative cyclization product was determined, and this step had to be conducted under the action of DPPA (entry 1). This difference illustrated that the coupling product from L-proline might have a favored conformation for direct condensative cyclization step. Using this two-step procedure, several 2-bromobenzylamines bearing electron-donating and electron-withdrawing groups were then checked. We were pleased to find that they provided the corresponding 1,4-benzoazepin-3-ones in moderate yields (entries 2–5). The additional functional groups in the benzene ring are ready for further conversions, and therefore allowing assembly of more diverse 1,4-benzoazepin-3-ones. Changing *N*-substituent had no influence to the reaction

Table 2
Synthesis of 1,4-benzoazepin-3-ones from other amino acids[a]



Entry	Product	Yield[b] (%)
1	 **6a**: Y = H, R = Bn	58
2	**6b**: Y=NO_2, R=Bn	44
3	**6c**: Y=OMe, R=Bn	35
4	**6d**: Y=F, R=Bn	48
5	**6e**: Y=CO_2Me, R=Bn	60
6	**6f**: Y=H, R=allyl	52
7	**6g**: Y=H, R=*n*-Bu	57
8	 **6h**	50[c]
9	 **6i**	51
10	 **6j**	46
11	 **6k**	40

[a] Reaction conditions: 2-bromobenzylamine (2 mmol), amino acid (3 mmol), CuI (0.2 mmol), Cs_2CO_3 (2 mmol), DMF (4 mL), 90 °C, 24 h, then DPPA (3 mmol), 0–5 °C, 8 h.
[b] Isolated yield.
[c] The ee value for **6h** was only 49%.

process, as evident from that 1,4-benzoazepin-3-ones **6f** and **6g** were isolated in 52–57% yields (entries 6 and 7). Four other amino acids were also compatible with this process (entries 8–11), although L-tryptophane and L-tyrosine gave slightly lower yields. Thus, we concluded that this method is suitable for preparing a considerable range of substituted 1,4-benzoazepin-3-ones.

2.3. Determination of the optical purity of the 1,4-benzodiazepin-3-ones

Because the coupling reaction was carried in the presence of base and at relatively high reaction temperatures, we wondered if racemization at this step. Accordingly, we attempted to determine the enantiomer excess values for all 1,4-benzoazepin-3-ones. However, only some of them were found applicable to chiral HPLC determination, and their enantiomer excess values were indicated in Table 3. It looked that no racemization took place for both L-proline and L-valine derived products, as they have greater than 99% ee. However, some racemization occurred for L-phenyl alanine

derived product and serious racemization was observed in case of L-alanine. These results demonstrated that steric hindrance plays an essential role for prevention of racemization. This trend is consistent to that observed in CuI-catalyzed coupling reaction of aryl halides and amino acids.[6a]

Table 3
The ee values of some 1,4-benzoazepin-3-ones[a]

Compound	5a	6f	6g	6i	6h
ee (%)	99	99	99	90	49

[a] Determined by chiral HPLC.

3. Conclusions

In summary, we have developed a CuI-catalyzed cascade process to synthesize 2-substituted 1,4-benzodiazepin-3-one. Changing the substituents at the benzene ring and N-position of 2-bromobenzylamines, and their amino acid coupling partners were demonstrated possible. Although in some cases partial racemization occurred, enantiopure products could be obtained by using L-proline and L-valine as the coupling partners. The present result provides another example to illustrate the potential for assembling heterocycles by using recently developed Ullmann-type coupling reaction conditions.[8]

4. Experimental

4.1. General remarks

All solvents were purified and dried prior to use. Optical rotations were measured by used a Perkin–Elmer 241MC polarimeter in the solvent indicated. ^{1}H NMR spectra were recorded at Bruker Avance 300 MHz, and ^{13}C NMR spectra were recorded at Bruker Avance 400 MHz, and assigned in parts per million (δ). ^{1}H NMR chemical shifts were given on the δ scale (ppm) and were referenced to internal TMS. Reference peaks for chloroform in ^{13}C NMR spectra were set at 77.0 ppm. For DMSO-d_6, the reference peaks in ^{1}H NMR and ^{13}C NMR spectra were set at 2.50 ppm and 40.0 ppm, respectively. Low-resolution mass spectra were recorded on a GILENT5973 instrument (EI) and a LCMS-2010EV instrument (ESI). High-resolution mass spectra were recorded on an IonSpec 4.7 Tesla FTMS instrument. Silica gel plate GF_{254} were used for thin layer chromatography (TLC) and silica gel H or 300–400 mesh were used for flash column chromatography. Enantiomeric excesses were determined by HPLC using a Daicel Chiralpak IB or IC-H column (wavelength=254 or 214 nm) with hexane/*i*-PrOH as the eluent.

4.2. General procedure for coupling of 2-halobenzyl-amines with L-proline

An oven-dried Schlenk tube was charged with 2-halobenzylamines **4** (2 mmol), L-proline (3.0 mmol), CuI (0.2 mmol), and cesium carbonate (2.0 mmol). The tube was evacuated and backfilled with argon, and then DMF (4 mL). After the mixture was stirred at 90 °C for 21 h and then 110 °C for 24 h under argon atmosphere, the cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give the corresponding tricyclic compound.

*4.2.1. (S)-5-Benzyl-1,2,3,3a,5,6-hexahydrobenzo[f]pyrrolo-[1,2-a][1,4]diazepin-4-one (**5a**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.34 (m, 5H), 7.14 (t, J=8.1 Hz, 1H), 6.76 (d, J=6.9 Hz, 1H), 6.48–6.56 (m, 2H), 5.30 (d, J=16.5 Hz, 1H), 5.17 (d, J=15.0 Hz, 1H), 5.07–5.10 (m, 1H), 4.19 (d, J=15.0 Hz, 1H), 3.71 (d, J=16.5 Hz, 1H), 3.29–3.38 (m, 2H), 2.65–2.70 (m, 1H), 1.95–2.13 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 146.2, 137.3, 129.4, 129.2, 128.5 (2C), 128.1 (2C), 127.3, 119.0, 115.8, 113.2, 58.7, 51.5, 49.6, 49.5, 28.0, 23.5; ESI-MS m/z 293.0 $(M+H)^+$; ESI-HRMS calcd for $C_{19}H_{21}N_2O$ $(M+H)^+$ m/z 293.1648, found 293.1645; HPLC: chiracel IB-H column (250 mm); detected at 254 nm; *n*-hexane/*i*-propanol: 90/10; flow: 0.7 mL/min; retention time: 16.5 min (major), 15.6 min (minor), ee=99%.

*4.2.2. (S)-5-Benzyl-8-nitro-3,3a,5,6-tetrahydro-1H-benzo-[f]pyrrolo[1,2-a][1,4]diazepin-4(2H)-one (**5b**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (dd, J=9.0, 2.7 Hz, 1H), 7.62 (d, J=2.7 Hz, 1H), 7.24–7.31 (m, 5H), 6.44 (d, J=9.0 Hz, 1H), 5.21–5.30 (m, 2H), 5.02 (d, J=14.7 Hz, 1H), 4.36 (d, J=14.7 Hz, 1H), 3.79 (d, J=16.8 Hz, 1H), 3.41–3.52 (m, 2H), 2.72–2.83 (m, 1H), 2.00–2.19 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.5, 151.1, 136.5, 129.3, 128.7 (2C), 128.3, 128.0, 127.8, 126.0, 125.6, 118.5, 112.5, 59.3, 50.7, 50.6, 49.6, 28.1, 23.4; EIMS m/z 333 (M^+); EI-HRMS calcd for $C_{19}H_{19}N_3O_3$ (M^+) m/z 333.1426, found 337.1433.

*4.2.3. (S)-5-Benzyl-8-methoxy-3,3a,5,6-tetrahydro-1H-benzo[f]-pyrrolo[1,2-a][1,4]diazepin-4(2H)-one (**5c**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.35 (m, 5H), 6.74 (dd, J=8.7, 2.7 Hz, 1H), 6.46 (d, J=8.7 Hz, 1H), 6.37 (d, J=2.7 Hz, 1H), 5.23 (d, J=16.5 Hz, 1H), 5.12 (d, J=15.0 Hz, 1H), 4.91–4.94 (m, 1H), 4.24 (d, J=15.0 Hz, 1H), 3.77 (d, J=16.5 Hz, 1H), 3.69 (s, 3H), 3.22–3.36 (m, 2H), 2.62–2.67 (m, 1H), 1.93–2.12 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 150.6, 140.8, 137.3, 128.6, 128.4, 128.2, 128.1, 127.4, 120.5, 115.9, 114.1, 114.0, 59.3, 55.9, 51.4, 49.9, 49.7, 28.1, 23.5. EIMS m/z 322 (M^+); EI-HRMS calcd for $C_{20}H_{22}N_2O_2$ (M^+) m/z 322.1681, found 322.1683.

*4.2.4. (S)-Methyl-5-benzyl-4-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[f]pyrrolo[1,2-a][1,4]diazepin-e-8-carboxylate (**5d**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, J=8.7, 1.8 Hz, 1H), 7.46 (d, J=1.8 Hz, 1H), 7.25–7.33 (m, 5H), 6.45 (d, J=8.7 Hz, 1H), 5.26 (d, J=16.5 Hz, 1H), 5.14–5.19 (m, 2H), 4.17 (d, J=14.7 Hz, 1H), 3.84 (s, 3H), 3.76 (d, J=16.5 Hz, 1H), 3.36–3.43 (m, 2H), 2.68–2.73 (m, 1H), 2.00–2.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.2, 150.0, 137.1, 131.6, 131.4, 128.9 (2C), 128.4 (2C), 127.8, 118.5, 117.0, 112.8, 59.1, 51.8, 51.4, 50.3, 49.7, 28.3, 23.7. EIMS m/z 350 (M^+); EI-HRMS calcd for $C_{21}H_{22}N_2O_3$ (M^+) m/z 350.1630, found 350.1633.

*4.2.5. (S)-5-Benzyl-8-fluoro-3,3a,5,6-tetrahydro-1H-benzo[f]-pyrrolo[1,2-a][1,4]diazepin-4(2H)-one (**5e**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.34 (m, 5H), 6.83 (td, J=8.4, 2.7 Hz, 1H), 6.46 (dd, J=9.0, 2.7 Hz, 1H), 6.39 (dd, J=9.0, 4.5 Hz, 1H), 5.23 (d, J=16.5 Hz, 1H), 5.04 (d, J=15.0 Hz, 1H), 4.96–4.99 (m, 1H), 4.28 (d, J=15.0 Hz, 1H), 3.66 (d, J=16.5 Hz, 1H), 3.23–3.33 (m, 2H), 2.62–2.68 (m, 1H), 1.94–2.11 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 154.1 (d, J=234 Hz), 142.6, 136.9, 128.5, 128.3, 128.0 (2C), 127.4, 120.0 (d, J=5.8 Hz), 115.8 (d, J=22.6 Hz), 115.1 (d, J=22.1 Hz), 113.6 (d, J=7.7 Hz), 58.8, 50.8, 49.8, 49.7, 27.9, 23.4; ESI-MS m/z 311 $(M+H)^+$; ESI-HRMS calcd for $C_{19}H_{20}N_2OF$ $(M+H)^+$ m/z 311.1554, found 311.1565.

*4.2.6. (S)-5-Allyl-3,3a,5,6-tetrahydro-1H-benzo[f]pyrrolo-[1,2-a][1,4]diazepin-4(2H)-one (**5f**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (td, J=8.4, 1.5 Hz, 1H), 6.86 (d, J=7.5 Hz, 1H), 6.57 (t, J=7.5 Hz, 1H), 6.48 (d, J=8.4 Hz, 1H), 5.68–5.81 (m, 1H), 5.35 (d, J=16.5 Hz, 1H), 5.14–5.22 (m, 2H), 5.01–5.04 (m, 1H), 4.32 (dd, J=15.3, 5.4 Hz, 1H), 3.91 (dd, J=15.3, 6.3 Hz, 1H), 3.77 (d, J=16.5 Hz, 1H), 3.23–3.37 (m, 2H), 2.57–2.66 (m, 1H), 1.91–2.09 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 146.0, 133.2, 129.2, 129.0, 119.0, 117.3, 115.2, 113.0, 58.4, 51.2, 49.3, 48.8, 27.7, 23.7; EIMS

m/*z* 242 (M^+); EI-HRMS calcd for $C_{15}H_{18}N_2O$ (M^+) *m*/*z* 242.1419, found 242.1410.

*4.2.7. (S)-5-Butyl-3,3a,5,6-tetrahydro-1H-benzo[f]pyrrolo-[1,2-a][1,4]diazepin-4(2H)-one (**5g**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (td, *J*=8.4, 1.8 Hz, 1H), 6.90 (dd, *J*=7.2, 1.2 Hz, 1H), 6.56 (t, *J*=7.2 Hz, 1H), 6.46 (d, *J*=8.1 Hz, 1H), 5.42 (d, *J*=16.5 Hz, 1H), 4.98–5.01 (m, 1H), 3.73 (d, *J*=16.5 Hz, 1H), 3.49–3.59 (m, 1H), 3.38–3.45 (m, 1H), 3.21–3.32 (m, 2H), 2.56–2.64 (m, 1H), 1.90–2.06 (m, 3H), 1.45–1.55 (m, 2H), 1.20–1.30 (m, 2H), 0.87 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 146.1, 129.2, 129.1, 119.5, 115.7, 113.1, 58.6, 52.5, 49.4, 46.9, 30.3, 27.9, 23.5, 20.0, 13.7; ESI-MS *m*/*z* 281 $(M+Na)^+$; ESI-HRMS calcd for $C_{16}H_{22}N_2ONa$ $(M+Na)^+$ *m*/*z* 281.1637, found 281.1624.

4.3. General procedure for coupling of 2-bromobenzylamines with other amino acids

An oven-dried Schlenk tube was charged with 2-bromobenzylamines **4** (2 mmol), α-amino acid (3.0 mmol), CuI (0.2 mmol), and Cs_2CO_3 (2.0 mmol). The tube was evacuated and backfilled with argon before DMF (4 mL) was added. After the mixture was stirred at 90 °C for 21 h, it was cooled to 4 °C, then DMF (6 mL) and DPPA (0.68 mL, 3 mmol) were added. The resultant solution was stirred at 0–4 °C overnight before it was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified via column chromatography to afford 1,4-benzodiazepin-3-ones.

*4.3.1. (S)-4-Benzyl-2-isopropyl-4,5-dihydro-1H-benzo[e]-[1,4]-diazepin-3(2H)-one (**6a**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.34 (m, 5H), 7.05 (td, *J*=8.4, 1.2 Hz, 1H), 6.74 (d, *J*=7.2 Hz, 1H), 6.55–6.58 (m, 2H), 5.06 (d, *J*=16.5 Hz, 1H), 5.00 (d, *J*=15.0 Hz, 1H), 4.35 (d, *J*=15.0 Hz, 1H), 4.18 (dd, *J*=6.3, 8.4 Hz, 1H), 3.86 (d, *J*=16.5 Hz, 1H), 3.72 (d, *J*=6.3 Hz, 1H), 2.22–2.34 (m, 1H), 1.13 (d, *J*=6.6 Hz, 3H), 1.12 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 145.6, 137.4, 129.5, 128.8, 128.5 (2C), 128.0 (2C), 127.3, 119.7, 117.7, 117.0, 61.3, 50.6, 49.7, 29.3, 20.4, 18.7; ESI-MS *m*/*z* 295 $(M+H)^+$; ESI-HRMS calcd for $C_{19}H_{23}N_2O$ $(M+H)^+$ *m*/*z* 295.1805, found 295.1809.

*4.3.2. (S)-4-Benzyl-2-isopropyl-7-nitro-4,5-dihydro-1H-benzo[e]-[1,4]diazepin-3(2H)-one (**6b**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, *J*=9.0, 2.4 Hz, 1H), 7.60 (d, *J*=2.4 Hz, 1H), 7.21–7.30 (m, 5H), 6.50 (d, *J*=9.0 Hz, 1H), 5.11 (d, *J*=16.5 Hz, 1H), 4.83 (d, *J*=14.7 Hz, 1H), 4.63 (d, *J*=5.4 Hz, 1H), 4.56 (d, *J*=14.7 Hz, 1H), 4.13 (dd, *J*=5.4, 8.7 Hz, 1H), 3.91 (d, *J*=16.5 Hz, 1H), 2.29–2.36 (m, 1H), 1.15 (d, *J*=6.6 Hz, 3H), 1.14 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.5, 153.4, 138.4, 135.8, 128.7 (2C), 128.2 (2C), 127.5, 126.9, 125.2, 118.8, 115.6, 60.0, 50.1, 49.6, 28.9, 20.3, 19.4; EIMS *m*/*z* 339 (M^+); EI-HRMS calcd for $C_{19}H_{21}N_3O_3$ (M^+) *m*/*z* 339.1583, found 339.1580.

*4.3.3. (S)-4-Benzyl-2-isopropyl-7-methoxy-4,5-dihydro-1H-benzo[e][1,4]diazepin-3(2H)-one (**6c**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.34 (m, 5H), 6.67 (dd, *J*=3.0, 8.4 Hz, 1H), 6.57 (d, *J*=8.4 Hz, 1H), 6.30 (d, *J*=3.0 Hz, 1H), 4.95 (d, *J*=14.7 Hz, 1H), 4.89 (d, *J*=16.5 Hz, 1H), 4.41 (d, *J*=14.7 Hz, 1H), 4.03 (d, *J*=7.2 Hz, 1H), 3.91 (d, *J*=16.5 Hz, 1H), 3.67 (s, 3H), 3.42 (br s, 1H), 2.25–2.32 (m, 1H), 1.12 (d, *J*=6.9 Hz, 3H), 1.11 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 152.1, 139.4, 137.3, 129.4, 128.4 (2C), 128.0 (2C), 127.3, 122.3, 118.9, 114.5, 62.3, 55.6, 50.4, 50.0, 29.7, 20.3, 18.5; ESI-MS *m*/*z* 325 $(M+H)^+$; ESI-HRMS calcd for $C_{20}H_{25}N_2O_2$ $(M+H)^+$ *m*/*z* 325.1911, found 325.1914.

*4.3.4. (S)-4-Benzyl-7-fluoro-2-isopropyl-4,5-dihydro-1H-benzo-[e][1,4]diazepin-3(2H)-one (**6d**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.32 (m, 5H), 6.77 (td, *J*=8.4, 3.0 Hz, 1H), 6.53 (dd, *J*=4.8, 8.7 Hz, 1H), 6.43 (dd, *J*=3.0, 8.7 Hz, 1H), 4.94 (d, *J*=16.2 Hz, 1H), 4.90 (d, *J*=15.0 Hz, 1H), 4.43 (d, *J*=15.0 Hz, 1H), 4.05–4.10 (m, 1H), 3.85 (d, *J*=16.2 Hz, 1H), 3.59 (d, *J*=6.6 Hz, 1H), 2.25–2.32 (m, 1H), 1.12 (d, *J*=6.6 Hz, 3H), 1.11 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 155.3 (d, *J*=237 Hz), 141.8 (d, *J*=2.4 Hz), 137.2, 128.5 (2C), 128.1 (2C), 127.4, 121.5 (d, *J*=6.4 Hz), 118.4 (d, *J*=7.5 Hz), 115.5 (d, *J*=22.3 Hz), 115.3 (d, *J*=21.3 Hz), 61.8, 50.1, 49.9, 29.5, 20.4, 18.6; ESI-MS *m*/*z* 335 $(M+Na)^+$; ESI-HRMS calcd for $C_{19}H_{21}FN_2ONa$ $(M+Na)^+$ *m*/*z* 335.1530, found 335.1539.

*4.3.5. (S)-Methyl-4-benzyl-2-isopropyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate (**6e**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, *J*=8.4, 2.1 Hz, 1H), 7.46 (d, *J*=2.1 Hz, 1H), 7.23–7.32 (m, 5H), 6.49 (d, *J*=8.4 Hz, 1H), 5.18 (d, *J*=16.5 Hz, 1H), 5.00 (d, *J*=15.0 Hz, 1H), 4.35 (d, *J*=15.0 Hz, 1H), 4.27 (d, *J*=8.4 Hz, 1H), 3.88 (d, *J*=16.5 Hz, 1H), 3.84 (s, 3H), 2.26–2.33 (m, 1H), 1.14 (d, *J*=6.3 Hz, 3H), 1.13 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 166.7, 149.7, 137.0, 131.8, 130.7, 128.6 (2C), 128.1 (2C), 127.5, 118.4, 118.0, 115.8, 60.9, 51.6, 50.4, 49.5, 29.2, 20.3, 18.7; EIMS *m*/*z* 352 (M^+); EI-HRMS calcd for $C_{21}H_{24}N_2O_3$ (M^+) *m*/*z* 352.1787, found 352.1786.

*4.3.6. (S)-4-Allyl-2-isopropyl-4,5-dihydro-1H-benzo[e][1,4]diazepin-3(2H)-one (**6f**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (td, *J*=7.5, 1.5 Hz, 1H), 6.88 (dd, *J*=7.8, 1.2 Hz, 1H), 6.62 (td, *J*=7.5, 0.9 Hz, 1H), 6.56 (dd, *J*=7.8, 0.9 Hz, 1H), 5.67–5.79 (m, 1H), 5.05–5.20 (m, 3H), 4.21–4.29 (m, 1H), 4.11 (d, *J*=8.4 Hz, 1H), 3.91–4.00 (m, 2H), 3.69 (br s, 1H), 2.20–2.28 (m, 1H), 1.11 (d, *J*=6.9 Hz, 3H), 1.08 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 145.6, 133.5, 129.6, 128.8, 119.8, 117.7, 117.3, 117.1, 61.3, 50.6, 49.1, 29.3, 20.3, 18.7; ESI-MS *m*/*z* 245 $(M+H)^+$; ESI-HRMS calcd for $C_{15}H_{21}N_2O$ $(M+H)^+$ *m*/*z* 245.16484, found 245.1654; HPLC: chiracel IB-H column (250 mm); detected at 254 nm; *n*-hexane/*i*-propanol: 90/10; flow: 0.7 mL/min; retention time: 8.2 min (major), 12.0 min (minor), ee=99%.

*4.3.7. (S)-4-Butyl-2-isopropyl-4,5-dihydro-1H-benzo[e][1,4]diazepin-3(2H)-one (**6g**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (t, *J*=7.8 Hz, 1H), 6.92 (d, *J*=7.5 Hz, 1H), 6.63 (t, *J*=7.5 Hz, 1H), 6.55 (d, *J*=7.8 Hz, 1H), 5.17 (d, *J*=16.5 Hz, 1H), 4.09 (dd, *J*=8.1, 6.3 Hz, 1H), 3.91 (d, *J*=16.5 Hz, 1H), 3.69 (d, *J*=6.3 Hz, 1H, N-H), 3.48 (t, *J*=7.2 Hz, 2H), 2.17–2.26 (m, 1H), 1.43–1.53 (m, 2H), 1.20–1.28 (m, 2H), 1.10 (t, *J*=7.2 Hz, 3H), 1.07 (t, *J*=7.2 Hz, 3H), 0.86 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 145.6, 129.3, 128.8, 120.2, 117.6, 117.0, 61.2, 51.7, 47.0, 30.4, 29.2, 20.4, 19.9, 18.6, 13.7; EIMS *m*/*z* 260 (M^+); EI-HRMS calcd for $C_{16}H_{24}N_2O$ (M^+) *m*/*z* 260.1889, found 260.1883; HPLC: chiracel IB-H column (250 mm); detected at 214 nm; *n*-hexane/*i*-propanol: 90/10; flow: 0.7 mL/min; retention time: 7.0 min (major), 10.7 min (minor), ee=99%.

*4.3.8. (S)-4-Benzyl-2-methyl-4,5-dihydro-1H-benzo[e][1,4]diazepin-3(2H)-one (**6h**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.30 (m, 5H), 7.05 (t, *J*=7.8 Hz, 1H), 6.73 (d, *J*=7.2 Hz, 1H), 6.49–6.59 (m, 2H), 5.23 (d, *J*=16.5 Hz, 1H), 5.07 (d, *J*=15.0 Hz, 1H), 4.82 (q, *J*=6.3 Hz, 1H), 4.30 (d, *J*=15.0 Hz, 1H), 3.72 (d, *J*=16.5 Hz, 1H), 1.46 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 145.6, 137.3, 129.6, 129.0, 128.6 (2C), 128.1 (2C), 127.4, 119.1, 117.5, 116.4, 50.7, 49.9 (2C), 17.4; ESI-MS *m*/*z* 267 $(M+H)^+$; ESI-HRMS calcd for $C_{17}H_{19}N_2O$ $(M+H)^+$ *m*/*z* 267.1492, found 267.1493; HPLC: chiracel IC-H column (250 mm); detected at 214 nm; *n*-hexane/*i*-propanol: 90/10; flow: 0.8 mL/min; retention time: 25.3 min (minor), 38.3 min (major), ee=49%.

*4.3.9. (S)-2,4-Dibenzyl-4,5-dihydro-1H-benzo[e][1,4]-diazepin-3(2H)-one (**6i**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.35 (m, 10H), 7.00 (t, J=8.4 Hz, 1H), 6.69 (d, J=7.2 Hz, 1H), 6.55 (t, J=8.4 Hz, 1H), 6.42 (d, J=8.1 Hz, 1H), 5.19 (d, J=16.5 Hz, 1H), 5.02 (d, J=15.0 Hz, 1H), 4.90 (m, 1H), 4.41 (d, J=15.0 Hz, 1H), 3.77 (d, J=16.5 Hz, 1H), 3.71 (br s, 1H), 3.46 (dd, J=14.7, 4.5 Hz, 1H), 2.97 (dd, J=14.7, 9.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 145.4, 137.5, 137.1, 129.3, 129.2, 128.8, 128.7 (2C), 128.5, 128.3 (2C), 128.1, 128.0, 127.3, 126.7, 119.6, 117.9, 116.7, 55.8, 50.6, 50.1, 37.5; ESI-MS m/z 343 $(M+H)^+$; ESI-HRMS calcd for $C_{23}H_{23}N_2O$ $(M+H)^+$ m/z 343.1805, found 343.1801; HPLC: chiracel IC-H column (250 mm); detected at 214 nm; *n*-hexane/*i*-propanol: 90/10; flow: 0.6 mL/min; retention time: 34.3 min (major), 36.3 min (minor), ee=90%.

*4.3.10. (S)-4-Benzyl-2-(4-hydroxybenzyl)-4,5-dihydro-1H-benzo-[e][1,4]diazepin-3(2H)-one (**6j**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14–7.32 (m, 9H), 6.99 (td, J=7.8, 1.5 Hz, 1H), 6.79 (d, J=8.7 Hz, 2H), 6.69 (d, J=7.8 Hz, 1H), 6.55 (td, J=7.5, 1.2 Hz, 1H), 6.42 (d, J=8.1 Hz, 1H), 5.16 (d, J=16.2 Hz, 1H), 4.98 (d, J=15.3 Hz, 1H), 4.84–4.86 (m, 1H), 4.43 (d, J=15.3 Hz, 1H), 3.78 (d, J=16.2 Hz, 1H), 3.71 (d, J=3.6 Hz, 1H), 3.33 (dd, J=14.1, 4.8 Hz, 1H), 2.88 (dd, J=14.1, 8.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.9, 156.1, 146.6, 138.5, 130.8 (2C), 130.0, 129.3, 128.7 (2C), 128.6, 128.0 (2C), 127.4, 119.7, 116.6, 116.4, 115.3 (2C), 55.4, 51.3, 49.9, 36.0; ESI-MS m/z 359 $(M+H)^+$; ESI-HRMS calcd for $C_{23}H_{23}N_2O_2$ $(M+H)^+$ m/z 359.1754, found 359.1761.

*4.3.11. (S)-2-((1H-Indol-3-yl)methyl)-4-benzyl-4,5-dihydro-1H-benzo[e][1,4]diazepin-3(2H)-one (**6k**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.69 (d, J=7.8 Hz, 1H), 7.13–7.41 (m, 9H), 6.99 (td, J=7.8, 1.2 Hz, 1H), 6.68 (d, J=6.0 Hz, 1H), 6.52 (t, J=7.5 Hz, 1H), 6.39 (d, J=7.5, 1H), 5.21 (d, J=16.5 Hz, 1H), 5.05 (d, J=15.0 Hz, 1H), 5.02 (m, 1H), 4.43 (d, J=15.0 Hz, 1H), 3.88 (br s, 1H), 3.74 (d, J=16.5 Hz, 1H), 3.53 (dd, J=15.0, 5.4 Hz, 1H), 3.18 (dd, J=15.0, 8.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.0, 146.8, 138.5, 136.6, 130.0, 129.0 (2C), 128.7, 128.3, 128.2, 128.0, 127.4, 124.3, 121.4, 119.6, 118.9, 118.8, 116.5, 116.4, 111.8, 111.3, 54.4, 51.3, 50.0, 26.9; ESI-MS m/z 404 $(M+Na)^+$; ESI-HRMS calcd for $C_{25}H_{23}N_3ONa$ $(M+Na)^+$ m/z 404.17333, found 404.1746.

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