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Diversity-oriented synthesis of 1,3-benzodiazepines

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ABSTRACT

A concise assembly of the 1,3-benzodiazepine core from A^3-coupling-derived propargylamines and *ortho*-bromophenylisocyanates is described. The developed synthetic sequence involves the addition of propargylamine to isocyanate followed by palladium-catalyzed intramolecular alkyne hydroarylation that could be accomplished in a stepwise or one-pot manner.

1. Introduction

Nitrogen-containing seven-membered heterocyclic systems such as 3-benzazepine[1] and 1,4-benzodiazepine[2] constitute a core structural elements of many natural and biologically active molecules and therefore could be rightfully designated as privileged structures (Fig. 1).[3] Fenoldopam, a representative 3-benzazepine-containing medication, is the first selective peripheral dopamine receptor agonist approved for clinical use for the treatment of severe hypertension.[4] Diazepam belongs to a large family of 1,4-benzodiazepine-based psychoactive drugs whose mechanism of action involves the enhancement of the inhibitory activity of the gamma-aminobutyric acid (GABA) neurotransmitter at the $GABA_A$ receptor, resulting in sedative, sleep-inducing, anxiolytic, alcohol withdrawal, anticonvulsant, and muscle relaxant therapeutic properties.[5]

1,3-Benzodiazepine skeleton, which results from a small structural deviation from the above scaffolds (Fig. 1), has been relatively less studied in terms of synthesis[6] and potential biological and therapeutic applications.[7] Therefore, we set a goal to develop a combinatorial route to provide a diversity-oriented entry to this medium-ring-containing class of heterocycles.

Recently, others and we made substantial efforts on exploiting A^3-coupling-derived propargylamines in heterocyclic chemistry.[8,9] Subjecting secondary propargylamines **1** to a palladium-catalyzed intramolecular alkyne hydroarylation process, we were able to attain a small set of 3-benzazepines **2** (Scheme 1).[10,11] Using primary propargylamines **3**, we have developed a series of protocols that selectively convert *in situ* generated propargylureas **4** into imidazol-2-ones **5**,[12,13] imidazolidin-2-ones **6**,[14] oxazolidin-2-imines **7**,[15] and pyrimidin-2-ones **8**[16] via silver- or gold-catalyzed cycloisomerizations (Scheme 1).

2. Results and discussion

Inspired by these processes, we envisaged that the 1,3-benzodiazepine core **9** could be assembled by a palladium-catalyzed intramolecular alkyne hydroarylation of propargylic

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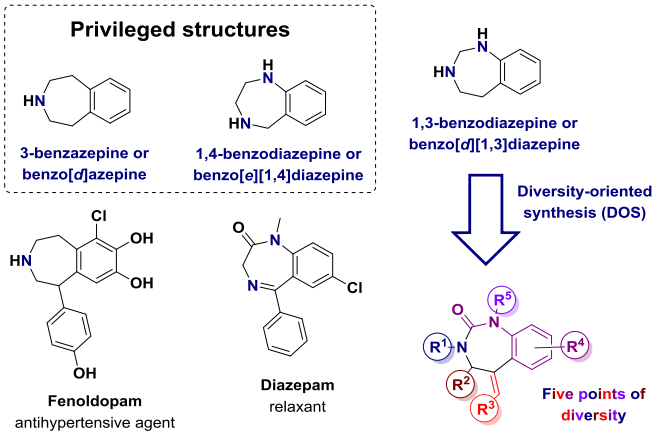
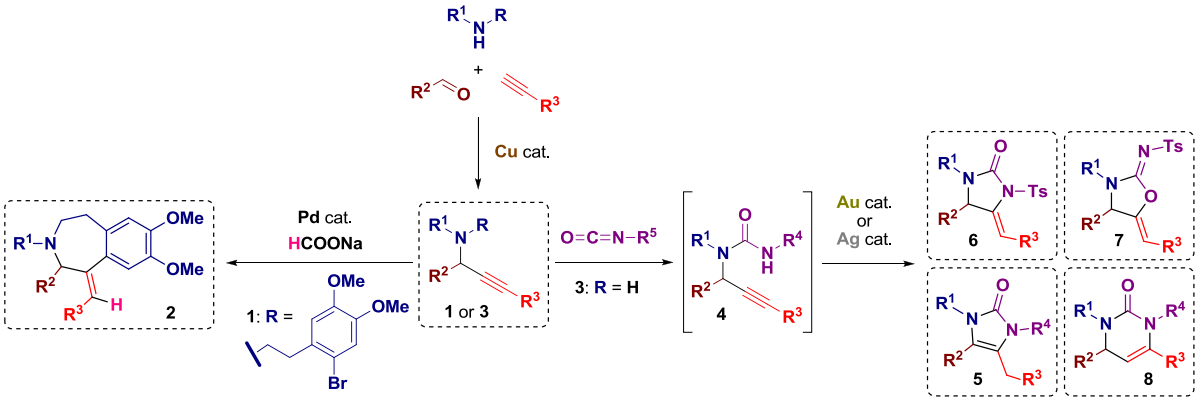


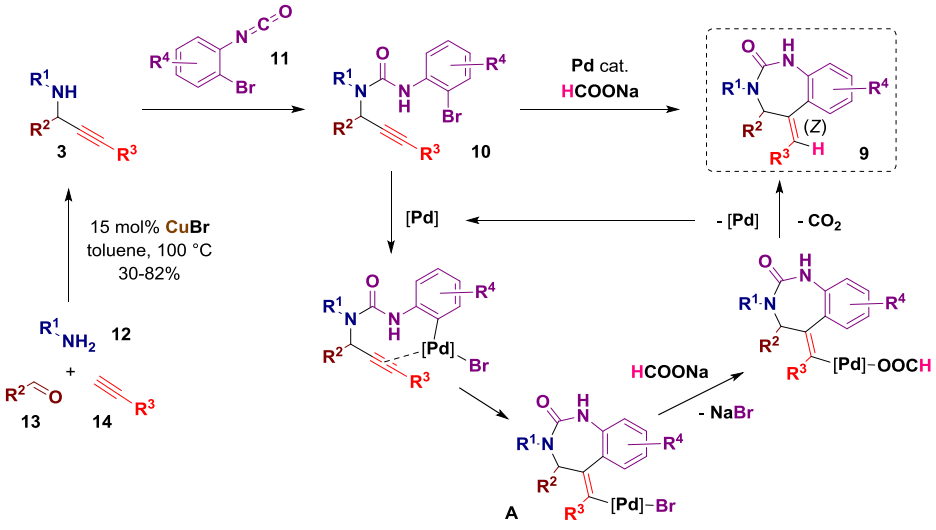
Fig. 1. Nitrogen-containing seven-membered heterocyclic systems.

ureas **10** derived from secondary propargylamines **3** and *ortho*-bromophenyl isocyanates **11** (Scheme 2). The proposed hydroarylation process involves an oxidative insertion of the Pd(0)-catalyst into the arylbromide moiety of **10**, followed by a triple bond carbopalladation and subsequent trapping of the resulting vinyl-palladium species **A** with sodium formate as reducing agent. The carbopalladation step is crucial for the whole process and allows to control the ring size and the double bond geometry in the forming 1,3-benzodiazepine product **9** (Scheme 2).[17] The required secondary propargylamines **3** are readily accessible from primary amines **12**, aldehydes **13** and terminal acetylenes **14** through a CuBr-catalyzed A^3-coupling protocol (Scheme 2).[18]

Reacting propargylamine **3a** with *ortho*-bromophenyl isocyanate (**11a**) gave propargylurea **10a** in 98% yield. In turn, this substrate was selected to perform the optimization of the Pd-catalyzed intramolecular alkyne hydroarylation that is also frequently referred to as reductive Heck reaction (Table 1). Conducting this transformation in DMF/H_2O mixtures that previously proved to be beneficial for such processes delivered desired 1,3-benzodiazepine **9a** albeit in low yield of maximum 38% (Table 1, entries 1–3). At the same time, this was accompanied by the degradation of significant amounts of urea **10a** back to the propargylamine **3a** (Table 1, entries 1–3). Using DMF or *i*PrOH as solvent gave no or little of **3a**, but the yield of target **9a** remained insufficient (Table 1, entries 4–6), despite some enhancement observed when reaction in DMF was conducted in the presence of phase-transfer catalyst (Table 1, entry 5). To our delight, the yield of **9a** was substantially improved by

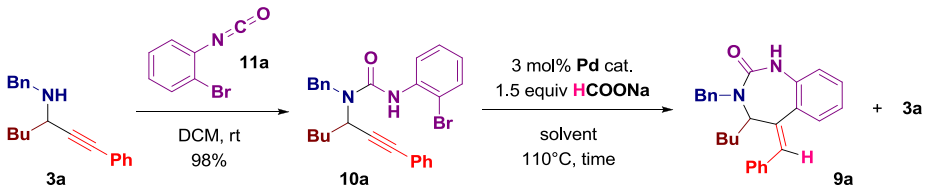


Scheme 1. Synthesis of various heterocycles from the A^3-coupling-derived propargylamines **1** and **3**.



Scheme 2. Strategy towards 1,3-benzodiazepines **9**.

Table 1
Optimization of the Pd-catalyzed intramolecular alkyne hydroarylation (reductive Heck) step.[a]

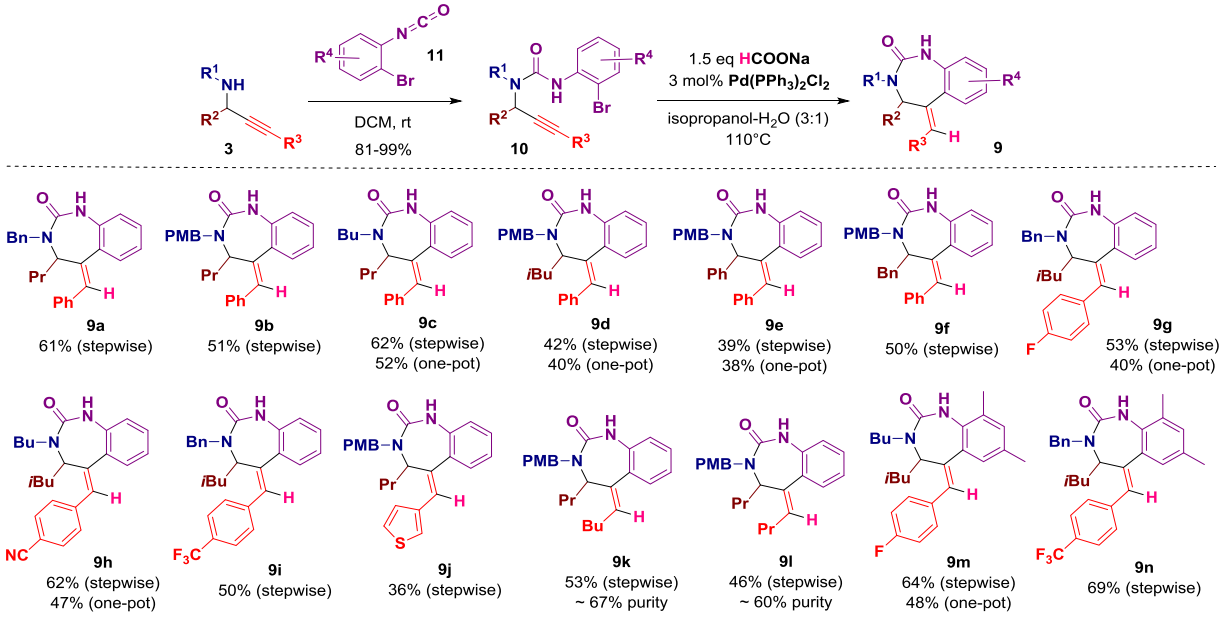


Entry	Catalyst	Solvent	Time, h	Yield, %[b]	
				9a	**3a**
1	$Pd(PPh_3)_4$	DMF/H_2O (3:1)	1	13	43
2	$Pd(PPh_3)_2Cl_2$	DMF/H_2O (3:1)	1	38	15
3	$Pd(PPh_3)_2Cl_2$	DMF/H_2O (9:1)	1	21	25
4	$Pd(PPh_3)_2Cl_2$	DMF	1	36	–
5[c]	$Pd(PPh_3)_2Cl_2$	DMF	2	46	–
6	$Pd(PPh_3)_2Cl_2$	*i*PrOH	4	34	9
7	$Pd(PPh_3)_2Cl_2$	*i*PrOH/H_2O (3:1)	4	62	26
8	$Pd(PPh_3)_2Cl_2$	*i*PrOH/H_2O (4:1)	4	57	14
9	$Pd(PPh_3)_2Cl_2$	*t*BuOH/H_2O (3:1)	4	55	18
10	3 mol% $Pd(OAc)_2$/6 mol% PPh_3	*i*PrOH/H_2O (3:1)	4	54	15
11	$Pd(PPh_3)_4$	*i*PrOH/H_2O (3:1)	4	28	38
12[d]	10 mol% $Ni(cod)_2$/20 mol% P(*n*Bu)$_3$	THF	18	–[e]	–

[a] The reactions were run at 110 °C on 0.25 mmol scale in 2 mL of solvent with 1.5 equiv od sodium formate as reducing agent.
[b] The yields of **9a** and **3a** were determined by ^{1}H NMR of the reaction mixture after work-up using 3,4,5-trimethoxybenzaldehyde as internal standard.
[c] The reaction was conducted in the presence of 1 equiv of tetra-butylammonium bromide (TBAB).
[d] The reaction was conducted at 100 °C in 0.5 mL of THF with 1.2 equiv of triethylsilane as reducing agent.
[e] 65% of unreacted **10a** was detected by ^{1}H NMR analysis of reaction mixture after removal of nickel catalyst by filtration through a short plug of silica gel. cod = 1,5-cyclooctadiene.

switching to *i*PrOH/H_2O or *t*BuOH/H_2O mixtures as the reaction media, although the competing degradation of **10a** into **3a** could not be completely suppressed (Table 1, entries 7–9). The best result was obtained for the reaction with $Pd(PPh_3)_2Cl_2$ as a catalyst and *i*PrOH/H_2O (3:1) as solvent producing **9a** in 62% yield as was determined by ^{1}H NMR analysis of reaction mixture (Table 1, entry 7). $Pd(OAc)_2$/PPh_3 and $Pd(PPh_3)_4$ showed lower efficiency under the same settings (Table 1, entries 10 and 11) while an attempt to utilize one of the literature protocols based on nickel catalysis[19] was completely unproductive (Table 1, entry 12).

Having effective conditions for the Pd-catalyzed alkyne hydroarylation step in hands, we moved to exploring the scope and limitations of our strategy (Scheme 3). The required propargylurea precursors **10** were obtained in high yields by reaction of propargylamines **3** with *ortho*-bromophenyl isocyanates **11**. The high efficiency of this transformation motivated us to compare the



Scheme 3. Scope of the Pd-catalyzed intramolecular alkyne hydroarylation leading to 1,3-benzodiazepine **9**.

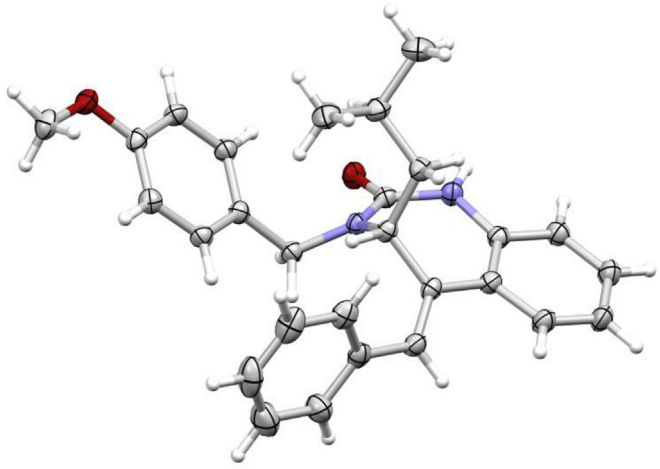


Fig. 2. X-ray crystallographic molecular structure of 1,3-benzodiazepine **9d**, showing thermal displacement ellipsoids at the 50% probability level.

sequential and one-pot approaches, when combining it with the final Pd-catalyzed alkyne hydroarylation process (Scheme 3). Using propargylureas **10a-j** bearing a (hetero)aromatic substituent on the triple-bond and with no additional substituents on the isocyanate-derived benzene ring (R^4 = H), the target 1,3-benzodiazepines **9a-j** were obtained in up to 62% and 52% for the stepwise and one-pot approaches, respectively. The structure of the representative 1,3-benzodiazepine **9d** was confirmed by X-ray crystallographic analysis (Fig. 2).[20] Conducting the Pd-catalyzed intramolecular alkyne hydroarylation with substrates **10k,l** bearing alkyl group on the triple-bond, led to an unclean reaction hampering the isolation of desired products **9k,l**. Thus, 1,3-benzodiazepines **9k,l** were obtained in a lower purity. The reactions of propargylureas **10m,n** derived from branched isocyanate **11b** (R^4 = 4,6-diMe) delivered 1,3-benzodiazepines **9m,n** in 64% and 69%, respectively (stepwise approach).

With not too many *ortho*-bromophenyl isocyanates **11** being commercially available, we turned our attention to the corresponding *ortho*-bromophenyl carboxylic acids **15a,b**. Reacting later with diphenylphosphoryl azide (DPPA) in the presence of triethylamine gave rise to the desired isocyanates **11c,d** through a Curtius rearrangement of initially formed acyl azides **16a,b**.[21] The reaction mixtures containing either **11c** or **11d** were directly treated with propargylamine **3c** allowing to attain propargylurea precursors **10o,p**. Finally, Pd-catalyzed cyclization afforded 1,3-benzodiazepines **9o,p** featuring electron donating or electron withdrawing R^4 substituents (Scheme 4).

It is important to stress, that despite the moderate efficiency in the Pd-catalyzed alkyne hydroarylation step, the overall synthetic sequence towards 1,3-benzodiazepines **9** starting from amines **12**, aldehydes **13** and acetylenes **14** proved to be operationally simple and robust. In fact, we have developed and implemented a practical exercise for the fourth year undergraduate students, which is based on this three-step methodology. The results obtained during 2016/2017 academic year at Soochow University, China demonstrate that the students from the intensive training class could satisfactorily reproduce the procedures described in this study with a minimal failure rate.[22]

In order to further extend the scope of our strategy and to introduce an additional diversity point into target 1,3-benzodiazepine scaffold, we evaluated a base-promoted N-alkylation reaction of **9** (Scheme 5a). Reacting 1,3-benzodiazepines **9** with benzyl chlorides **17** or with methyl iodide (**18**) in the presence of sodium hydride smoothly produced alkylated 1,3-benzodiazepines **19** in up to 96%. Another viable synthetic manipulation involved an acid-promoted removal of the *para*-methoxybenzyl group[23] from the substrate **9f** to afford 1,3-benzodiazepine **20** containing two unprotected NH groups (Scheme 5b left). Interestingly, an analogous transformation of **9e** bearing phenyl group at the allylic position was accompanied by a double-bond migration leading to the formation of isomerized 1,3-benzodiazepine **21** (Scheme 5b right).

3. Conclusion

In summary, we have developed a diversity-oriented strategy towards 1,3-benzodiazepines that involves a one-pot or sequential reaction of A^3-coupling-derived propargylamines with *ortho*-bromophenylisocyanates, followed by a palladium-catalyzed intramolecular alkyne hydroarylation. An additional N-alkylation step further enriches the overall strategy allowing to construct a 1,3-benzodiazepine core featuring five points of diversity.

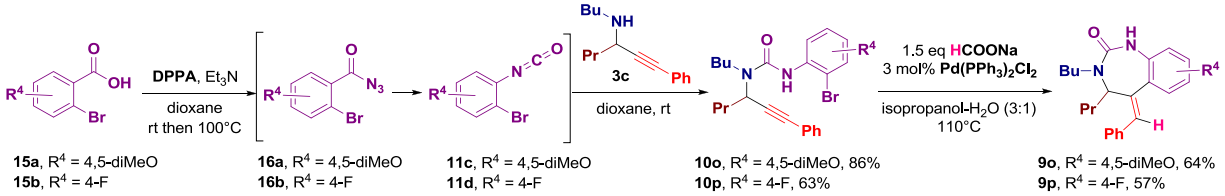
4. Experimental

4.1. General information

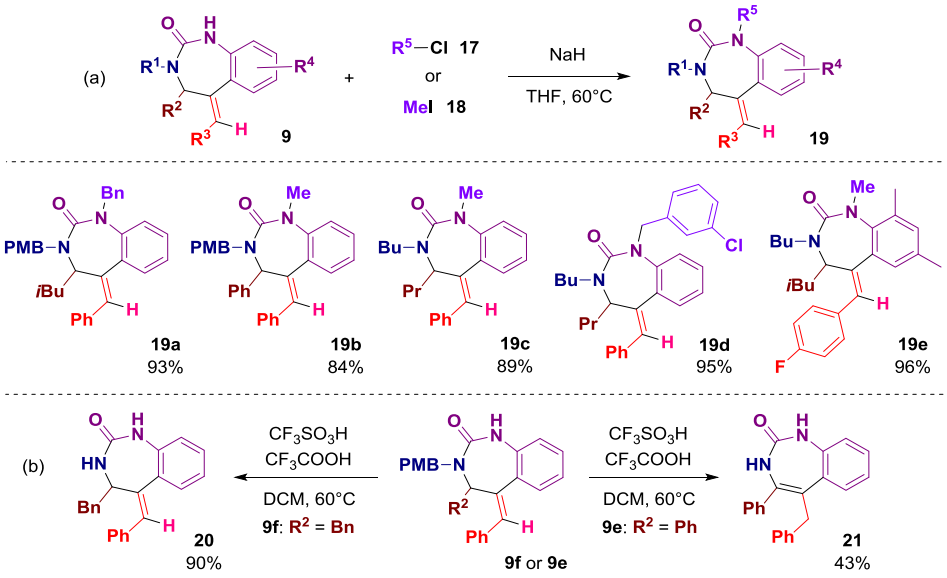
All starting materials and solvents were purchased from commercial sources and used as received. Melting points were measured using INESA WRR apparatus. Infrared (FT-IR) spectra were recorded neat on a Bruker Vertex 70. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded using a Bruker Avance III HD instrument. The ^{1}H and ^{13}C chemical shifts are reported relative to TMS using the residual $CDCl_3$ signal as internal reference. HRMS were performed on a Bruker micrOTF-Q III.

4.2. General procedure for the synthesis of secondary propargylamines **3**

Copper (I) bromide catalyst (17 mg, 0.12 mmol) was placed in a screw cap vial followed by addition of dry toluene (1.0 mL), amine **12** (0.8 mmol), aldehyde **13** (1 mmol), and phenyl acetylene **14** (1.6 mmol). The resulting mixture was flushed with argon, sealed and stirred at 100 °C for 5 h. Upon completion of this time, the mixture was diluted with ethyl acetate and transferred to the round bottom flask. Then the silicagel was added and the mixture was concentrated under reduced pressure. Column chromatography on



Scheme 4. Extended scope of the Pd-catalyzed intramolecular alkyne hydroarylation leading to 1,3-benzodiazepine **9**.



Scheme 5. Base-promoted alkylation of **9** and PMB-deprotection of **9f** and **9e**.

silica gel using petroleum ether-ethyl acetate (9:1 → 8:2) mixture as eluent provided pure propargylamine **3**.

4.3. General procedure for the synthesis of propargylureas *10a-n*

Propargylamine **3** (0.7 mmol) was placed in a screw cap vial followed by addition of dry DCM (2.8 mL) and *ortho*-bromophenyl isocyanate **11** (1.05 mmol). The resulting mixture was sealed and stirred at rt for 0.5 h. Upon completion of this time, the mixture was diluted with ethyl acetate and transferred to the round bottom flask. Then the silicagel was added and the mixture was concentrated under reduced pressure. Column chromatography on silica gel using petroleum ether-ethyl acetate (49:1 → 9:1) mixture as eluent provided pure propargylurea **10**.

4.4. General procedure for the synthesis of propargylureas *10o,p*[21c]

2-Bromobenzoic acid **15** (2.5 mmol) was placed in a screw cap vial followed by addition of dry dioxane (6 mL), diphenylphosphoryl azide (DPPA, 688 mg, 2.5 mmol) and triethylamine (273 mg, 2.7 mmol). The resulting mixture was sealed and stirred at rt for 1 h followed by heating at 100 °C for another 2 h. Then propargylamine **3c** (459 mg, 2 mmol) in dry dioxane (4 mL) was added and the mixture was continued to stir at rt for 1 h. Upon completion of this time, the mixture was diluted with ethyl acetate and transferred to the round bottom flask. Then the silicagel was added and the mixture was concentrated under reduced pressure. Column chromatography on silica gel using petroleum ether-ethyl acetate (9:1 for **10o**; 47:3 for **10p**) mixture as eluent provided pure propargylurea **10**.

4.5. General procedure for the synthesis of 1,3-benzodiazepines *9* through the Pd-catalyzed intramolecular alkyne hydroarylation

Propargylurea **10** (0.5 mmol), bis(triphenylphosphine)palladium(II) dichloride (10.5 mg, 0.015 mmol) and sodium formate (51 mg, 0.75 mmol) were placed to the screw cap vial followed by addition of isopropanol (3 mL) and water (1 mL). The resulting mixture was flushed with argon, sealed and stirred at 100 °C for 4 h. Upon completion of this time, the mixture was diluted with ethyl acetate and transferred to the round bottom flask. Then the silicagel was added and the mixture was concentrated under reduced pressure. Column chromatography on silica gel using petroleum ether-ethyl acetate (9:1 → 8:2 → 1:1) mixture as eluent provided 1,3-benzodiazepine **9**.

4.6. General procedure for the one-pot synthesis of 1,3-benzodiazepines *9*

Propargylamine **3** (0.5 mmol) was placed in a screw cap vial followed by addition of dry DCM (2 mL) and *ortho*-bromophenyl isocyanate **11** (0.75 mmol). The resulting mixture was sealed and stirred at rt for 0.5 h. Upon completion of this time, the vial was open and the DCM was evaporated under the ambient condition. The crude propargylurea **10** was transferred to the next step. Bis(-triphenylphosphine)palladium(II) dichloride (10.5 mg, 0.015 mmol) and sodium formate (51 mg, 0.75 mmol) were added to the vial with the crude urea **10** followed by addition of isopropanol (3 mL) and water (1 mL). The resulting mixture was flushed with argon, sealed and stirred at 100 °C for 4 h. Upon completion of this time, the mixture was diluted with ethyl acetate and transferred to the round bottom flask. Then the silicagel was added and the mixture was concentrated under reduced pressure. Column chromatography on silica gel using petroleum ether-ethyl acetate (9:1 → 8:2 → 1:1) mixture as eluent provided 1,3-benzodiazepine **9**.

4.6.1. (Z)-3-Benzyl-5-benzylidene-4-propyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (*9a*)

Yield: 61% (stepwise from **10a**); beige solid; mp: 127–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (bs, 1H), 7.44–7.33 (m, 4H), 7.27–7.12 (m, 6H), 7.03–6.94 (m, 2H), 6.91–6.82 (m, 3H), 4.87 (d, J = 14.5 Hz, 1H), 4.49 (dd, J = 8.8, 7.0 Hz, 1H), 3.70 (d, J = 14.5 Hz, 1H), 1.51–1.21 (m, 2H), 1.10–0.78 (m, 2H), 0.57 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 139.3, 137.7, 137.6, 137.2, 129.6, 129.1, 128.94, 128.92, 128.5, 128.3, 128.0, 127.4, 127.2, 125.3, 121.7, 118.6, 54.5, 53.9, 33.7, 19.5, 13.8; IR (ATR, neat): ν 3210, 3066, 3023, 2960, 2926, 2860, 1655, 1576, 1474, 1454, 1432, 1339, 1281, 1260, 1219, 830, 755, 721, 697 cm^{-1}; HRMS (ESI, $[M+H]^+$) for $C_{26}H_{27}N_2O^+$ calcd. 383.2118, found 383.2116.

*4.6.2. (Z)-5-Benzylidene-3-(4-methoxybenzyl)-4-propyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9b**)*

Yield: 51% (stepwise from **10b**); white solid; mp: 220–222 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (bs, 1H), 7.45–7.32 (m, 4H), 7.26–7.16 (m, 3H), 7.03–6.92 (m, 2H), 6.91–6.74 (m, 3H), 6.68 (d, J = 8.5 Hz, 2H), 4.81 (d, J = 14.4 Hz, 1H), 4.49 (t, J = 7.8 Hz, 1H), 3.77 (s, 1H), 3.64 (d, J = 14.4 Hz, 1H), 1.50–1.26 (m, 2H), 1.12–0.82 (m, 2H), 0.59 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 156.7, 139.2, 137.7, 136.9, 130.3, 129.8, 129.7, 129.2, 129.0, 128.6, 128.1, 127.3, 125.3, 121.9, 118.3, 113.7, 55.3, 54.1, 53.1, 33.7, 19.6, 13.9; IR (ATR, neat): ν 3325, 3210, 3071, 3022, 2960, 2926, 2853, 1655, 1614, 1575, 1511, 1474, 1436, 1323, 1305, 1281, 1233, 1305, 1281, 1233, 1220, 1173, 1029, 831, 761, 754, 699, 688, 658 cm^{-1}; HRMS (ESI, $[M+Na]^+$) for $C_{27}H_{28}N_2O_2Na^+$ calcd.435.2043, found 435.2055.

*4.6.3. (Z)-5-Benzylidene-3-butyl-4-propyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9c**)*

After column chromatography, product **9c** was additionally purified by washing with diethyl ether. Yield: 62% (stepwise from **10c**), 52% (one-pot from **3c** and **11a**); white solid; mp: 243–245 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (bs, 1H), 7.45–7.35 (m, 3H), 7.34–7.17 (m, 4H), 7.01–6.94 (m, 1H), 6.94–6.87 (m, 2H), 4.57 (t, J = 7.9 Hz, 1H), 3.46–3.32 (m, 1H), 3.11–2.97 (m, 1H), 1.75–1.61 (m, 1H), 1.61–1.48 (m, 1H), 1.45–1.20 (m, 3H), 1.20–1.01 (m, 4H), 0.84 (t, J = 7.3 Hz, 3H), 0.71 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 139.6, 137.5, 137.1, 129.7, 129.0, 128.9, 128.6, 128.3, 127.3, 125.3, 121.6, 118.2, 55.7, 51.2, 34.3, 30.3, 20.0, 19.9, 14.2, 13.7; IR (ATR, neat): ν 3218, 3116, 3077, 3020, 2958, 2933, 2872, 1656, 1577, 1476, 1462, 1434, 1361, 1302, 1219, 1074, 817, 749, 699, 661 cm^{-1}; HRMS (ESI, $[M+H]^+$) for $C_{23}H_{29}N_2O$ calcd. 349.2274, found 349.2256.

*4.6.4. (Z)-5-Benzylidene-4-isobutyl-3-(4-methoxybenzyl)-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9d**)*

After column chromatography, product **9d** was additionally purified by washing with diethyl ether. Yield: 42% (stepwise from **10d**), 40% (one-pot from **3d** and **11a**); white solid; mp: 223–226 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (bs, 1H), 7.48–7.32 (m, 4H), 7.25–7.16 (m, 3H), 7.05–6.90 (m, 3H), 6.84 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 4.89 (d, J = 14.4 Hz, 1H), 4.52 (t, J = 7.0 Hz, 1H), 3.78 (s, 3H), 3.74 (d, J = 14.5 Hz, 1H), 1.38–1.19 (m, 3H), 0.58 (d, J = 5.8 Hz, 3H), 0.49 (d, J = 5.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 157.1, 139.7, 137.7, 137.1, 130.4, 129.8, 129.6, 129.2, 128.9, 128.5, 127.8, 127.2, 125.5, 121.8, 118.5, 113.7, 55.4, 53.1, 52.8, 40.8, 24.9, 22.7, 22.6; IR (ATR, neat): ν 3210, 3071, 3022, 2960, 2902, 1655, 1615, 1576, 1510, 1475, 1435, 1323, 1238, 1218, 1172, 1030, 834, 766, 755, 698, 659 cm^{-1}; HRMS (ESI, $[M+Na]^+$) for $C_{28}H_{30}N_2O_2Na^+$ calcd. 449.2199, found 449.2197.

*4.6.5. (Z)-5-Benzylidene-3-(4-methoxybenzyl)-4-phenyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9e**)*

After column chromatography, product **9e** was additionally purified by washing with diethyl ether. Yield: 39% (stepwise from **10e**), 38% (one-pot from **3e** and **11a**); beige solid; mp: 246–248 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.47 (m, 2H), 7.36–7.28 (m, 3H), 7.26–7.17 (m, 3H), 7.15–7.06 (m, 4H), 7.05–6.99 (m, 2H), 6.98–6.90 (m, 1H), 6.80 (d, J = 8.5 Hz, 2H), 6.68–6.58 (m, 3H), 5.87 (s, 1H), 4.70 (d, J = 14.4 Hz, 1H), 4.01 (d, J = 14.4 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 157.5, 138.5, 137.4, 137.2, 136.4, 130.6, 129.7, 129.2, 129.0, 128.84, 128.82, 128.80, 128.2, 127.5, 127.0, 126.1, 125.8, 122.0, 118.8, 113.8, 57.53, 55.26, 53.00; IR (ATR, neat): ν 3212, 3077, 3026, 2832, 1661, 1577, 1510, 1472, 1436, 1302, 1237, 1218, 1174, 1028, 824, 766, 750, 737, 698, 655 cm^{-1}; HRMS (ESI, $[M+Na]^+$) for $C_{30}H_{26}N_2O_2Na^+$ calcd. 469.1886, found 469.1878.

*4.6.6. (Z)-4-Benzyl-5-benzylidene-3-(4-methoxybenzyl)-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9f**)*

After column chromatography, product **9f** was additionally purified by washing with diethyl ether. Yield: 50% (stepwise from **10f**); white solid; mp: 212–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99–7.78 (m, 1H), 7.43–7.36 (m, 1H), 7.33–7.26 (m, 2H), 7.26–7.19 (m, 2H), 7.19–7.11 (m, 3H), 7.10–7.02 (m, 1H), 7.00–6.93 (m, 1H), 6.89 (s, 1H), 6.78–6.68 (m, 4H), 6.61–6.54 (m, 2H), 6.54–6.46 (m, 2H), 4.91 (d, J = 14.3 Hz, 1H), 4.55 (dd, J = 10.6, 4.4 Hz, 1H), 3.81 (s, 3H), 3.42 (d, J = 14.3 Hz, 1H), 2.86 (dd, J = 12.8, 10.8 Hz, 1H), 2.44 (dd, J = 13.0, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 156.7, 138.0, 137.3, 137.0, 130.5, 130.1, 129.6, 129.5, 129.2, 129.0, 128.7, 128.4, 128.3, 127.1, 126.7, 125.2, 122.1, 118.6, 113.8, 55.7, 55.4, 52.7, 38.5; IR (ATR, neat): ν 3219, 3079, 2961, 2923, 2851, 1656, 1606, 1577, 1509, 1462, 1438, 1352, 1297, 1236, 1221, 1176, 1031, 831, 765, 758, 746, 701 cm^{-1}; HRMS (ESI, $[M+Na]^+$) for $C_{31}H_{28}N_2O_2Na^+$ calcd. 483.2043, found 483.2034.

*4.6.7. (Z)-3-Benzyl-5-(4-fluorobenzylidene)-4-isobutyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9g**)*

Yield: 53% (stepwise from **10g**), 40% (one-pot from **3g** and **11a**); beige solid; mp: 208–211 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (bs, 1H), 7.38 (dd, J = 7.8, 1.2 Hz, 1H), 7.26–7.15 (m, 4H), 7.11–6.96 (m, 5H), 6.96–6.91 (m, 2H), 6.86 (s, 1H), 6.84 (dd, J = 8.1, 0.6 Hz, 1H), 4.49–4.40 (m, 1H), 4.44 (t, J = 7.3 Hz, 1H), 3.97 (d, J = 14.6 Hz, 1H), 1.36–1.21 (m, 3H), 0.56 (d, J = 6.1 Hz, 3H), 0.50 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0 (d, J = 247.0 Hz), 157, 139.8, 137.6, 137.0, 133.5 (d, J = 3.4 Hz), 130.7 (d, J = 7.9 Hz), 129.6, 129.1, 128.9, 128.4, 127.6, 127.0, 125.4, 121.9, 118.5 (d, J = 1.3 Hz), 115.46 (d, J = 21.4 Hz), 54.0, 53.4, 40.9, 24.9, 22.7, 22.6; IR (ATR, neat): ν 3213, 3068, 2952, 2923, 2868, 1657, 1579, 1504, 1473, 1454, 1431, 1329, 1286, 1218, 1155, 832, 757, 745, 730, 700, 657, 618 cm^{-1}; HRMS (ESI, $[M+Na]^+$) for $C_{27}H_{27}FN_2ONa^+$ calcd. 437.2000, found 437.2007.

*4.6.8. (Z)-4-((3-Butyl-4-isobutyl-2-oxo-1,2,3,4-tetrahydro-5H-benzo[d][1,3]diazepin-5-ylidene)methyl)benzonitrile (**9h**)*

Yield: 62% (stepwise from **10h**), 47% (one-pot from **3i** and **11a**); beige solid; mp: 236–238 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (bs, 1H), 7.71 (d, J = 7.9 Hz, 2H), 7.42–7.32 (m, 3H), 7.29–7.20 (m, 1H), 7.04–6.91 (m, 2H), 6.86 (s, 1H), 4.50 (t, J = 7.3 Hz, 1H), 3.52–3.37 (m, 1H), 3.11–2.97 (m, 1H), 1.72–1.50 (m, 2H), 1.44–1.31 (m, 1H), 1.23–1.04 (m, 4H), 0.91–0.79 (m, 6H), 0.75 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 142.4, 142.2, 137.2, 132.4, 129.7, 129.61, 129.55, 125.7, 124.6, 121.8, 118.7, 118.5, 111.0, 54.4, 51.5, 41.2, 30.4, 25.1, 23.1, 22.9, 20.0, 13.8; IR (ATR, neat): ν 3198, 3056, 2955, 2933, 2866, 2223, 1653, 1603, 1580, 1500, 1486, 1474, 1436, 1362, 1339, 1308, 1228, 876, 832, 781, 746, 662 cm^{-1}; HRMS (ESI, $[M+H]^+$) for $C_{25}H_{30}N_3O$ calcd. 388.2383, found 388.2364.

*4.6.9. (Z)-3-Benzyl-4-isobutyl-5-(4-(trifluoromethyl)benzylidene)-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9i**)*

After column chromatography, product **9i** was additionally purified by washing with diethyl ether. Yield: 50% (stepwise from **10i**); white solid; mp: 232–235 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.51 (m, 3H), 7.44–7.36 (m, 1H), 7.31–7.09 (m, 6H), 7.05–6.97 (m, 1H), 6.90 (s, 1H), 6.89–6.77 (m, 3H), 4.71 (d, J = 14.7 Hz, 1H), 4.42 (t, J = 7.3 Hz, 1H), 3.97 (d, J = 14.7 Hz, 1H), 1.48–1.22 (m, 3H), 0.60 (d, J = 6.2 Hz, 3H), 0.51 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 141.2, 141.0, 137.2, 137.1, 129.7, 129.5, 129.3 (q, J = 32.5 Hz), 128.8, 128.5, 127.7, 126.3, 125.5 (q, J = 3.7 Hz), 125.0, 124.3 (q, J = 271.9 Hz), 122.0, 118.6, 53.9, 53.1, 40.8, 25.0, 22.8, 22.6; IR (ATR, neat): ν 3327, 3205, 3112, 3068, 2966, 2957, 2936, 2902, 2872, 1655, 1580, 1508, 1472, 1456, 1436, 1361, 1321, 1226, 1160, 1107, 1067, 1017, 884, 875, 831, 818, 751, 731, 701, 668 cm^{-1}; HRMS (ESI, $[M+Na]^+$) for $C_{28}H_{27}F_3N_2ONa^+$ calcd.

487.1968, found 487.1959.

4.6.10. (Z)-3-(4-Methoxybenzyl)-4-propyl-5-(thiophen-3-ylmethylene)-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9j**)

Yield: 36% (stepwise from **10j**); beige solid; mp: 206–208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (bs, 1H), 7.41–7.32 (m, 2H), 7.26–7.18 (m, 1H), 7.03–6.89 (m, 5H), 6.83–6.79 (m, 1H), 6.78 (s, 1H), 6.74 (d, J = 8.5 Hz, 2H), 4.76 (d, J = 14.5 Hz, 1H), 4.61 (dd, J = 8.7, 7.0 Hz, 1H), 3.87 (d, J = 14.5 Hz, 1H), 3.79 (s, 3H), 1.51–1.32 (m, 2H), 1.13–0.84 (m, 2H), 0.62 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 157.0, 139.2, 138.2, 136.9, 130.1, 129.8, 129.6, 128.97, 128.95, 125.8, 125.3, 123.2, 122.4, 121.9, 118.5, 113.8, 55.3, 54.7, 53.4, 33.7, 19.6, 13.9; IR (ATR, neat): ν 3322, 3220, 3114, 3079, 2990, 2968, 2936, 1656, 1606, 1577, 1509, 1462, 1437, 1352, 1297, 1236, 1221, 1176, 1031, 831, 765, 758, 746, 702 cm^{-1}; HRMS (ESI, [M+Na]$^+$) for $C_{25}H_{26}N_2O_2SNa^+$ calcd. 441.1607, found 441.1597.

4.6.11. (Z)-3-(4-Methoxybenzyl)-5-pentylidene-4-propyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9k**)

The isolated product was contaminated with unidentified impurities. Yield: 53% (67% purity, stepwise from **10k**); washing with diethyl ether can improve the purity but leads to significant loses of **9k**; yield after wash: 32% (78% purity); white solid; mp: 185–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (bs, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.20–7.10 (m, 2H), 6.94–6.82 (m, 3H), 6.81–6.75 (m, 1H), 5.68 (t, J = 7.3 Hz, 1H), 4.89 (d, J = 14.8 Hz, 1H), 4.48 (d, J = 14.8 Hz, 1H), 4.24 (dd, J = 8.9, 6.8 Hz, 1H), 3.80 (s, 3H), 1.91–1.77 (m, 1H), 1.70–1.59 (m, 1H), 1.47–1.36 (m, 2H), 1.29–1.17 (m, 4H), 1.06–0.92 (m, 2H), 0.90–0.83 (m, 3H), 0.68 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 156.1, 136.6, 136.1, 131.5, 130.2, 129.8, 129.4, 128.3, 126.6, 121.9, 117.8, 114.1, 55.4, 54.6, 53.3, 34.0, 32.1, 27.8, 22.6, 19.4, 14.1, 13.7; IR (ATR, neat): ν 3198, 3058, 2962, 2932, 2861, 1653, 1581, 1512, 1461, 1434, 1336, 1249, 1226, 1176, 1036, 853, 830, 760, 732, 689 cm^{-1}; HRMS (ESI, [M+Na]$^+$) for $C_{25}H_{32}N_2O_2Na^+$ calcd. 415.2356, found 415.2348.

4.6.12. (Z)-5-Butylidene-3-(4-methoxybenzyl)-4-propyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9l**)

The isolated product was contaminated with unidentified impurities. Yield: 46% (60% purity, stepwise from **10l**); washing with diethyl ether can improve the purity but leads to significant loses of **9l**; yield after wash: 25% (78% purity); beige solid; mp: 163–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (bs, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.21–7.10 (m, 2H), 6.94–6.81 (m, 4H), 5.68 (t, J = 7.2 Hz, 1H), 4.91 (d, J = 14.8 Hz, 1H), 4.50 (d, J = 14.8 Hz, 1H), 4.24 (dd, J = 9.1, 6.5 Hz, 1H), 3.80 (s, 3H), 1.87–1.75 (m, 1H), 1.70–1.58 (m, 1H), 1.47–1.36 (m, 2H), 1.36–1.23 (m, 2H), 1.05–0.94 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H), 0.68 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 156.3, 136.8, 136.4, 131.2, 130.3, 129.9, 129.2, 128.3, 126.6, 121.7, 118.0, 114.1, 55.4, 54.6, 53.3, 34.0, 30.1, 23.1, 19.3, 14.0, 13.7; IR (ATR, neat): ν 3200, 3062, 2957, 2930, 2859, 1654, 1613, 1581, 1512, 1487, 1462, 1435, 1334, 1309, 1248, 1228, 1175, 1037, 853, 828, 762, 734, 689 cm^{-1}; HRMS (ESI, [M+Na]$^+$) for $C_{24}H_{30}N_2O_2Na^+$ calcd. 401.2199, found 401.2201.

4.6.13. (Z)-3-Butyl-5-(4-fluorobenzylidene)-4-isobutyl-7,9-dimethyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9m**)

Yield: 64% (stepwise from **10m**), 48% (one-pot from **3h** and **11b**); beige solid; mp: 168–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.15 (m, 2H), 7.13–7.04 (m, 2H), 7.02 (s, 1H), 6.96 (s, 1H), 6.80 (s, 1H), 6.63 (bs, 1H), 4.50 (t, J = 7.2 Hz, 1H), 3.48–3.33 (m, 1H), 3.09–2.96 (m, 1H), 2.29 (s, 3H), 2.27 (s, 3H), 1.61–1.47 (m, 2H), 1.38–1.02 (m, 5H), 0.86–0.78 (m, 6H), 0.73 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0 (d, J = 247.2 Hz), 155.3, 140.6, 133.5 (d, J = 3.5 Hz), 132.7, 131.7, 130.6, 130.5 (d, J = 7.9 Hz), 128.4, 127.3, 125.7, 123.3, 115.5 (d, J = 21.5 Hz), 54.4, 51.4, 41.7, 30.4, 25.0, 22.91, 22.90, 20.5, 20.0, 18.5, 13.7; IR (ATR, neat): ν 3225, 2959, 2927, 2870, 1641, 1505, 1465, 1430, 1317, 1220, 863, 836, 821, 781, 744, 612 cm^{-1}; HRMS (ESI, [M+Na]$^+$) for $C_{26}H_{33}FN_2ONa^+$ calcd. 431.2469, found 431.2473.

4.6.14. (Z)-3-Benzyl-4-isobutyl-7,9-dimethyl-5-(4-(trifluoromethyl)benzylidene)-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9n**)

Yield: 69% (stepwise from **10n**); beige solid; mp: 147–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 8.1 Hz, 2H), 7.23–7.10 (m, 5H), 7.06 (s, 1H), 7.01 (s, 1H), 6.91–6.83 (m, 3H), 6.78 (s, 1H), 4.67 (d, J = 14.6 Hz, 1H), 4.41 (t, J = 7.2 Hz, 1H), 4.07 (d, J = 14.6 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 1.42–1.19 (m, 3H), 0.60 (d, J = 6.1 Hz, 3H), 0.54 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 141.3, 141.2, 137.2, 132.7, 132.1, 131.0, 129.3, 129.2 (d, J = 32.6 Hz), 128.8, 128.5, 128.4, 127.6, 126.9, 125.5, 125.4 (q, J = 3.7 Hz), 124.3 (d, J = 272.0 Hz), 123.7, 53.7, 53.2, 41.0, 24.9, 22.6, 22.6, 20.5, 18.5; IR (ATR, neat): ν 3306, 3240, 2959, 2926, 2869, 1637, 1455, 1322 1292, 1163, 1125, 1103, 1066, 1017, 907, 862, 841, 760, 734, 714, 700 cm^{-1}; HRMS (ESI, [M+Na]$^+$) for $C_{30}H_{31}F_3N_2ONa^+$ calcd. 515.2281, found 515.2280.

4.6.15. (Z)-5-Benzylidene-3-butyl-7,8-dimethoxy-4-propyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9o**)

Yield: 64% (stepwise from **10o**); brown solid; mp: 183–184 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.76 (bs, 1H), 7.46–7.38 (m, 2H), 7.34–7.24 (m, 3H), 6.90 (s, 2H), 6.83 (s, 1H), 4.52 (t, J = 7.8 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.35–3.24 (m, 1H), 2.85–2.74 (m, 1H), 1.72–1.58 (m, 1H), 1.57–1.43 (m, 1H), 1.41–1.17 (m, 2H), 1.02–0.87 (m, 4H), 0.82 (t, J = 7.3 Hz, 3H), 0.61 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.2, 149.4, 143.5, 138.5, 137.4, 131.2, 128.7, 128.4, 126.9, 125.3, 115.8, 112.0, 102.3, 55.8, 55.3, 54.4, 49.8, 33.5, 29.6, 19.27, 19.25, 14.0, 13.4; IR (ATR, neat): ν 3342, 3212, 3090, 2950, 2929, 2857, 1664, 1444, 1251, 861, 697 cm^{-1}; HRMS (ESI, [M+H]$^+$) for $C_{25}H_{33}N_2O_3^+$ calcd. 409.2486, found 409.2478.

4.6.16. (Z)-5-Benzylidene-3-butyl-7-fluoro-4-propyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**9p**)

Yield: 57% (stepwise from **10p**); beige solid; mp: 187–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (s, 1H), 7.48–7.40 (m, 2H), 7.37–7.27 (m, 3H), 7.23 (dd, J = 10.1, 2.7 Hz, 1H), 7.18–7.04 (m, 2H), 6.99 (s, 1H), 4.52 (t, J = 7.8 Hz, 1H), 3.33–3.21 (m, 1H), 2.92–2.79 (m, 1H), 1.69–1.53 (m, 1H), 1.53–1.39 (m, 1H), 1.38–1.12 (m, 2H), 1.04–0.86 (m, 4H), 0.79 (t, J = 7.3 Hz, 3H), 0.61 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.7 (d, J = 237.0 Hz), 154.7, 137.9 (d, J = 1.4 Hz), 136.8, 134.0 (d, J = 1.9 Hz), 128.7, 128.5, 127.3, 125.8 (d, J = 7.3 Hz), 119.5 (d, J = 8.1 Hz), 115.8 (d, J = 22.7 Hz), 114.8 (d, J = 22.9 Hz), 54.2, 49.8, 33.5, 29.6, 19.3, 19.2, 13.9, 13.4; IR (ATR, neat): ν 3334, 3221, 3102, 3065, 2957, 2931, 2872, 1660, 1475, 1222, 1189, 862, 828, 763, 700 cm^{-1}; HRMS (ESI, [M+H]$^+$) for $C_{23}H_{28}FN_2O^+$ calcd. 367.2180, found 367.2167.

4.7. General procedure for the synthesis of 1,3-benzodiazepines 19 by base-promoted alkylation of **9**

1,3-Benzodiazepine **9** (0.3 mmol) was placed in a screw cap vial followed by addition of dry THF (1 mL), sodium hydride (19.2 mg, 60% dispersion in mineral oil, 0.48 mmol) and benzyl chloride **17** (0.6 mmol) or methyl iodide (**18**, 85 mg, 0.6 mmol). The resulting mixture was sealed and stirred at 60 °C for 3 h. Upon completion of this time, the mixture was diluted with ethyl acetate and transferred to the round bottom flask. Then the silicagel was added and the mixture was concentrated under reduced pressure. Column chromatography on silica gel using petroleum ether-ethyl acetate

(9:1 → 8:2) mixture as eluent provided pure 1,3-benzodiazepine **19**.

*4.7.1. (Z)-1-Benzyl-5-benzylidene-4-isobutyl-3-(4-methoxybenzyl)-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**19a**)*

Yield: 93%; white solid; mp: 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.26 (m, 3H), 7.26–7.08 (m, 11H), 7.00–6.94 (m, 2H), 6.79 (d, J = 8.6 Hz, 2H), 6.70 (s, 1H), 5.18 (d, J = 15.4 Hz, 1H), 4.96 (d, J = 15.4 Hz, 1H), 4.60–4.49 (m, 2H), 4.27 (d, J = 14.6 Hz, 1H), 3.82 (s, 3H), 1.65–1.54 (m, 1H), 1.43–1.30 (m, 1H), 1.18–1.06 (m, 1H), 0.59 (d, J = 6.6 Hz, 3H), 0.42 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 159.0, 141.7, 139.2, 138.8, 136.7, 134.7, 130.5, 130.3, 130.1, 128.6, 128.6, 128.5, 128.3, 127.7, 127.1, 126.8, 124.5, 121.7, 113.9, 58.6, 55.4, 55.1, 51.7, 42.1, 24.6, 23.1, 22.0; IR (ATR, neat): ν 3029, 2954, 2931, 2865, 1615, 1509, 1454, 1413, 1242, 1200, 1174, 1031, 770, 759, 700, 692 cm^{-1}; HRMS (ESI, $[M+H]^+$) for $C_{35}H_{37}N_2O_2^+$ calcd. 517.2850, found 517.2860.

*4.7.2. (Z)-5-Benzylidene-3-(4-methoxybenzyl)-1-methyl-4-phenyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**19b**)*

Yield: 84%; white solid; mp: 144–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.17 (m, 5H), 7.13–7.05 (m, 5H), 7.05–6.94 (m, 5H), 6.85–6.78 (m, 2H), 6.74 (d, J = 8.6 Hz, 2H), 5.71 (s, 1H), 4.28 (d, J = 14.3 Hz, 1H), 4.17 (d, J = 14.3 Hz, 1H), 3.79 (s, 3H), 3.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 159.1, 141.6, 140.0, 136.7, 136.6, 131.0, 130.8, 129.4, 128.84, 128.75, 128.6, 128.4, 128.2, 127.3, 127.0, 125.8, 123.4, 119.8, 113.8, 61.2, 55.3, 51.0, 37.8; IR (ATR, neat): ν 2954, 2922, 2853, 1649, 1607, 1508, 1493, 1458, 1446, 1299, 1258, 1235, 1172, 1098, 1033, 851, 765, 749, 737, 725, 703, 609 cm^{-1}; HRMS (ESI, $[M+H]^+$) for $C_{31}H_{29}N_2O_2^+$ calcd. 461.2224, found 461.2231.

*4.7.3. (Z)-5-Benzylidene-3-butyl-1-methyl-4-propyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**19c**)*

Yield: 89%; yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, J = 7.7, 1.3 Hz, 1H), 7.43–7.35 (m, 2H), 7.35–7.25 (m, 4H), 7.15–7.03 (m, 2H), 6.92 (s, 1H), 4.49 (t, J = 7.6 Hz, 1H), 3.31 (s, 3H), 3.20–3.07 (m, 2H), 1.88–1.73 (m, 1H), 1.47–1.18 (m, 5H), 1.18–1.04 (m, 2H), 0.79 (t, J = 7.2 Hz, 3H), 0.76 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 141.5, 139.3, 137.4, 130.4, 128.8, 128.7, 128.52, 128.45, 127.9, 127.2, 122.9, 119.1, 58.9, 50.4, 38.0, 34.9, 30.2, 20.1, 19.5, 14.0, 13.8; IR (ATR, neat): ν 2957, 2928, 2871, 1649, 1596, 1459, 1447, 1300, 1233, 1118, 1096, 1033, 753, 700 cm^{-1}; HRMS (ESI, $[M+H]^+$) for $C_{24}H_{31}N_2O^+$ calcd. 363.2431, found 363.2443.

*4.7.4. (Z)-5-Benzylidene-3-butyl-1-(3-chlorobenzyl)-4-propyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**19d**)*

Yield: 95%; yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.33 (m, 2H), 7.33–7.19 (m, 6H), 7.17–7.03 (m, 5H), 6.78 (s, 1H), 5.11 (d, J = 15.6 Hz, 1H), 4.91 (d, J = 15.6 Hz, 1H), 4.41 (dd, J = 8.6, 5.2 Hz, 1H), 3.34–3.20 (m, 1H), 3.19–3.05 (m, 1H), 1.71–1.56 (m, 1H), 1.52–1.35 (m, 2H), 1.25–0.94 (m, 5H), 0.81 (t, J = 7.3 Hz, 3H), 0.68 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 141.5, 141.2, 139.2, 136.7, 134.6, 134.2, 130.7, 129.6, 128.8, 128.61, 128.59, 128.4, 127.46, 127.45, 126.9, 125.6, 124.5, 121.4, 62.1, 54.7, 50.4, 35.8, 30.5, 20.3, 19.0, 14.0, 13.9; IR (ATR, neat): ν 2957, 2930, 2871, 1626, 1596, 1576, 1455, 1355, 1286, 1241, 1210, 1077, 760, 699, 683 cm^{-1}; HRMS (ESI, $[M+H]^+$) for $C_{30}H_{34}ClN_2O^+$ calcd. 473.2354, found 473.2362.

*4.7.5. (Z)-3-Butyl-5-(4-fluorobenzylidene)-4-isobutyl-1,7,9-trimethyl-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**19e**)*

Yield: 96%; white solid; mp: 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.19 (m, 2H), 7.08–6.96 (m, 3H), 6.85 (s, 1H), 6.73 (s, 1H), 4.21 (dd, J = 10.9, 2.5 Hz, 1H), 3.54–3.39 (m, 1H), 3.12 (s, 3H), 2.87–2.70 (m, 1H), 2.33 (s, 3H), 2.25 (s, 3H), 1.59–1.42 (m, 2H), 1.40–1.04 (m, 4H), 0.98–0.82 (m, 4H), 0.69 (d, J = 6.7 Hz, 3H), 0.39 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1 (d, J = 246.9 Hz), 161.0, 139.4, 138.8, 136.8, 135.7, 132.6, 132.5 (d, J = 3.4 Hz), 131.5, 130.5 (d, J = 8.0 Hz), 129.4, 125.5115.51 (d, J = 21.4 Hz), 63.0, 48.1, 42.0, 38.8, 30.8, 24.4, 24.0, 21.1, 20.9, 20.6, 18.6, 14.0; IR (ATR, neat): ν 2957, 2925, 2858, 1642, 1626, 1603, 1507, 1466, 1459, 1447, 1367, 1343, 1279, 1220, 1157, 1146, 1078, 858, 830, 817, 787, 759 cm^{-1}; HRMS (ESI, $[M+H]^+$) for $C_{27}H_{36}FN_2O^+$ calcd. 423.2806, found 423.2819.

*4.8. General procedure for PMB-deprotection of 1,3-benzodiazepines **9f,e**[23]*

1,3-Benzodiazepine **9f** (92 mg, 0.2 mmol) was placed in a screw cap vial followed by addition of DCM (1.5 mL), trifluoroacetic acid (0.5 mL) and triflic acid (12 μL). The resulting mixture was sealed and stirred at 50 °C for 3 h. Upon completion of this time, the mixture was diluted with ethyl acetate and transferred to the round bottom flask. Then the silicagel was added and the mixture was concentrated under reduced pressure. Column chromatography on silica gel using petroleum ether-ethyl acetate (1:1) mixture as eluent provided 1,3-benzodiazepine **20**. Starting from **9e** (45 mg, 0.1 mmol), 1,3-benzodiazepine **21** was obtained following the same procedure and using petroleum ether-ethyl acetate (9:1 → 8:2) mixture as eluent for column chromatography.

*4.8.1. (Z)-4-Benzyl-5-benzylidene-1,3,4,5-tetrahydro-2H-benzo[d][1,3]diazepin-2-one (**20**)*

Yield: 90%; white solid; mp: 154–155 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.10 (bd, J = 1.5 Hz, 1H), 7.58 (dd, J = 7.2, 1.7 Hz, 1H), 7.37–7.14 (m, 9H), 7.14–7.08 (m, 2H), 7.02–6.94 (m, 1H), 6.93–6.85 (m, 2H), 6.73 (m, 1H), 4.52 (q, J = 7.4 Hz, 1H), 2.76 (dd, J = 13.4, 7.3 Hz, 1H), 2.64 (dd, J = 13.4, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.4, 139.4, 137.9, 137.4, 136.6, 129.8, 129.0, 128.8, 128.6, 128.3, 128.2, 127.8, 127.1, 126.3, 126.2, 121.3, 118.1, 50.0, 40.3; IR (ATR, neat): ν 3215, 3027, 1683, 1480, 1421, 1231, 746, 697 cm^{-1}; HRMS (ESI, $[M+H]^+$) for $C_{23}H_{21}N_2O^+$ calcd. 341.1648, found 341.1638.

*4.8.2. 5-Benzyl-4-phenyl-1,3-dihydro-2H-benzo[d][1,3]diazepin-2-one (**21**)*

Yield: 43%; beige solid; mp: 179–180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79–7.73 (m, 1H), 7.68 (bs, 1H), 7.52–7.36 (m, 7H), 7.29–7.17 (m, 3H), 7.16–7.06 (m, 4H), 4.06–4.00 (m, 2H), ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.5, 140.7, 135.92, 135.85, 131.9, 129.2, 128.32, 128.28, 128.24, 128.0, 127.9, 125.9, 123.3, 121.1, 119.3, 115.5, 112.6, 29.6; IR (ATR, neat): ν 3464, 3291, 3178, 2921, 1678, 1604, 1452, 1388, 1338, 740, 698 cm^{-1}; HRMS (ESI, $[M+H]^+$) for $C_{22}H_{19}N_2O^+$ calcd. 327.1492, found 327.1479.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.09.034.

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