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One-Pot Synthesis of Seven-Membered Heterocyclic Derivatives of Diazepines Involving Copper-Catalyzed Rearrangement Cascade Allyl-Amination

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Abstract

A novel and efficient method has been proposed for the synthesis of 1,4-benzodiazepine-5-ones from *o*-nitrobenzoic *N*-allylamides by using molybdenyl acetylacetonate and copper(II) trifluoromethanesulfonate as catalysts in the presence of triphenylphosphine. This synthesis process involves nitrene formation, C–H bond insertion, C=C bond rearrangement, and C–N bond formation cascade reactions via copper- and molybdenum-catalyzed mediation. The method features a wide substrate scope and a moderate to high yield (up to 90%), exhibiting the possibility for practical applications.

Graphical Abstract

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Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.9b02710>.

Crystallographic information of compound **2z** (CIF)

¹H and ¹³C{¹H} NMR spectra, additional reaction schemes, X-ray single crystal data, and larger scale reaction schemes (PDF)

Complete contact information is available at: <https://pubs.acs.org/doi/10.1021/acs.joc.9b02710>

The authors declare no competing financial interest.

- One-pot synthesis of 1,4-benzodiazepine-5-one derivatives
- Strategy via nitrene formation, C-H insertion, C-N formation and C=C rearrangement
- 27 samples, moderate to high yields (up to 90%)

INTRODUCTION

The construction of 1,4-benzodiazepine-5-one derivatives has practical application value in the development of new drugs.¹ Compounds containing a benzodiazepine nucleus are of great significance in the study of pharmacology,² attracting the attention of many scientists.^{3,4} In the past few decades, these compounds have explicitly exhibited fascinating biological activities, such as anti-HIV,⁵ antibacterial,^{6,7} antianxiety,^{8,9} antithrombosis,¹⁰ antioxidation,¹¹ and antihypertension,¹² and they are also used in the treatment of ischemic injury,¹³ as muscle relaxants,¹⁴ and for diabetes insipidus.¹⁵ In recent years, more attractive molecules, including broad-spectrum antitumor antibiotics (e.g., anthramycin^{16,17} and diazepam¹⁸), BRD4 inhibitors (e.g., GSK525762A¹⁹), and anticonvulsant agents (e.g., GABA_A agonist²⁰) have been discovered (Figure 1).

Over the past decades, some syntheses of the benzodiazepine skeleton have been reported (Scheme 1, previous work). The first method of constructing seven-membered heterocycles was through C–C bond formation by photocatalytic decarboxylation of the substrate and intramolecular C–C coupling containing carbonyl groups.²¹ The C–C bond was formed by the electrophilic substitution of the benzene ring by Fischer alkylation or acylation, and the coupling reaction catalyzed by palladium was carried out under a CO atmosphere. The second method was through C–N formation, such as the nucleophilic substitution reaction of the amino *p*-benzene ring,²² or the intramolecular S_N2 nucleophilic substitution reaction of the amino group to the halogenated alkyl group.²³ The C–N bond could also be constructed by the condensation reaction between the amino group and carbonyl group,²⁴ such as Liu Carter-like condensation reaction between the amine group and carboxylic acid derivatives²⁵ and Pictet–Spengler-like reaction²⁶ of phenylalkylamine derivatives and aldehydes.²⁴ For example, the Broggini group achieved regioselective formation of seven-membered diazepinone rings by intramolecular Pd-catalyzed amination of *N*-allylanthranilamides and the C–H activation method.²⁷

The Wolfe group synthesized saturated 1,4-benzodiazepines via Pd-catalyzed carboamination reactions with construction of C–C and C–N bonds simultaneously.²⁸ The Grunewald team prepared a series of benzodiazepinone derivatives which acted as selective inhibitors of the EC 2.1.1.28 enzyme from 2,3-dihydroquinolin-4(1*H*)-one by means of azide insertion.²⁹ The Santagada group developed microwave enhanced solution synthesis of 1,4-benzodiazepin-5-ones from aromatic primary amines or azides and olefins.³⁰ The Doemling group developed diverse 1,4-benzodiazepine scaffolds by Ugi-four-component reactions.³¹ As part of our interest in the synthesis of seven-membered heterocyclic

derivatives of diazepines, we herein report the one-pot synthesis of 1,4-benzodiazepine-5-ones with wide substrate scope and moderate to high yields (Scheme 1, this work).

RESULTS AND DISCUSSION

Initially, we began to investigate the best reaction conditions by using *N*-(furan-2-ylmethyl)-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide **1aa**, PPh₃, and MoO₂Cl₂(dmf)₂ under refluxing toluene conditions (Table 1). To our delight, the target compound 4-(furan-2-ylmethyl)-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5*H*-benzo[e][1,4]diazepin-5-one **2a** was obtained, but the yield was only 20%, and the majority of aniline derivative **3a** was produced as a byproduct (entry 2). Next, we screened a series of Mo catalysts and found that Mo acetylacetonate may be the most effective catalyst (entry 3). At the same time, the Mo group metal catalysts, tungsten hexacarbonyl, and chromium acetylacetonate were examined, and they could not initiate the formation of the target product (entries 14 and 15). Subsequently, we expanded the screening range of the catalysts, including bis(2,4-pentanedionic acid) platinum(II), bis(triphenylphosphine) nickel chloride, iron acetate, Pd(OAc)₂, CuCl₂, Ru₃(CO)₁₂, and Rh-(CO)₂(C₅H₇O₂), respectively, but could not deliver the target compound (entry 7–13). To increase the yield, we used two catalysts to promote the reactions. When MoO₂Cl₂(dmf)₂ and CuCl₂ were used together, the yield of the target product was increased to 45% (entry 16). Fortunately, when we combined MoO₂(acac)₂ with Cu(CF₃SO₃)₂, the yield of the target product was increased to 90% (entry 1), and only traces of the aniline derivative were detected. With the optimal catalyst in hand, we investigated the solvent effect on this reaction, and different solvents, including dichloromethane, tetrahydrofuran, acetone, acetonitrile, *N,N*-dimethylformamide, and dimethyl sulfoxide, have been compared with refluxing in the presence of MoO₂(acac)₂, Cu(CF₃SO₃)₂, and PPh₃. The experimental results showed that the reaction did not occur in those solvents (entries 18–22). Therefore, we decided to use MoO₂(acac)₂ and Cu(CF₃SO₃)₂ as catalysts and anhydrous toluene as solvent in the atmosphere of N₂ at 110 °C. We then screened reductants, and the yield of the target product was 90% when PPh₃ was used (entry 1). Regrettably, its yields were only 43 and 51% when using S-(–)-BINAP and xantphos, respectively (entries 24 and 25). The reaction did not occur by applying trimethylphosphine or when no reductant was used (entries 23 and 26). In addition, the reaction temperature and time were also investigated using MoO₂(acac)₂ and Cu(CF₃SO₃)₂ as catalysts, anhydrous toluene as solvent, and PPh₃ as reductant under N₂ atmosphere. When the reaction temperature was varied from 30 to 60 °C, no desired product appeared (entries 27 and 28). The desired compound was produced when the temperature reached 80 °C (entry 29), and the yield of the product was over 85% when the temperature was increased to 110 or 140 °C (entries 29 and 30). Furthermore, we found that prolonging reaction time could increase the yields, but the yield was almost same when the other reaction conditions were unchanged from 12 to 16 h (entries 31–33). Finally, the reaction was completed successfully at 110 °C for 12 h using substrate **1aa** (0.16 mmol), MoO₂(acac)₂ (10 mol %), Cu(CF₃SO₃)₂ (10 mol %), PPh₃ (2.5 equiv), and toluene (2 mL), respectively.

Based on the optimized conditions, the scope and generality of a series of 1,4-benzodiazepine-5-one derivatives were then evaluated. As shown in Table 2, the reaction could proceed well to afford corresponding products in moderate to high yields. The

structure was further ambiguously confirmed by single crystal X-ray synthesis of compound **2z** (Figure 2).

To comprehend the reaction well, we performed a series of experiments to observe the special effects of different substrates on the synthesis (Scheme 2). The effect of C–H activation with rearrangement of the double bond on the reaction was first investigated. Under standard reaction conditions, the ratio of hydrogen to deuterium between the corresponding product obtained by the reaction and the starting material of the reaction remained unchanged (Scheme 2, reaction 1). Meanwhile, in the presence of methyl on the side chain alkene, the reaction could still obtain a yield of 80% (reaction 2). The results showed that the carbon-hydro activation of alkene hydrogen was not necessary. They also suggested that the double bond migration occurred prior to the C–N bond formation. To confirm this point, reaction 3 was tested (Scheme 2, reaction 3). The reaction did not occur, and the corresponding cyclization products were not detected.

On the basis of our experimental results and the previous mechanism investigations, it is speculated that $\text{MoO}_2(\text{acac})_2$ is necessary for the reaction, and $\text{Cu}(\text{CF}_3\text{SO}_3)_2$ can significantly increase the yield of the reaction. Therefore, a plausible mechanism is suggested that starting from substrate **1a**, $\text{MoO}_2(\text{acac})_2$ interacts with PPh_3 to reduce the nitro group of the substrate **1a** to the nitrene intermediate **c** and with the participation of $\text{Cu}(\text{CF}_3\text{SO}_3)_2$ to form the N–Cu bond. Next, the double bond carbon and allyl hydrogen form a cyclohexanic intermediate **d**. Then, the allyl hydrogen was removed, and the double bond was rearranged at the same time to form the N–H bond and give the intermediate **e**. Finally, the target compound **2a** was obtained and catalyst $\text{Cu}(\text{CF}_3\text{SO}_3)_2$ was released. In short, we postulated the mechanism as shown in Scheme 3. The novel diazepine synthesis possibly occurred via reduction of the nitro group, followed by the removal of allyl-hydrogen in the presence of divalent copper Cu (II) and rearrangement of double bond.

CONCLUSIONS

In summary, we successfully developed an efficient one-pot strategy for the construction of 1,4-benzodiazepine-5-ones from the derivatives of *N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide by using $\text{MoO}_2(\text{acac})_2$ and $\text{Cu}(\text{CF}_3\text{SO}_3)_2$ as cocatalyst. The tandem annulation procedure involves the reduction of the nitro group, the formation of nitrene, C–H activation, and the formation of cyclohexanic intermediate, followed by the removal of allyl-hydrogen in the presence of divalent copper Cu(II). Then, rearrangement of the double bond and a subsequent intramolecular cyclization process occur. This catalytic system exhibits good functional group tolerance. We preliminarily explored the antineoplastic activity of these compounds, which could be important intermediates in the synthesis of some biologically active seven-membered nitrogen heterocycle compounds, and further research is underway. We expect that this approach could be widely used in the formation of various heterocyclic frameworks in our future research.

EXPERIMENTAL SECTION

General Methods.

NMR experiments were accomplished on a 400 or 600 MHz spectrometer. Column chromatography was performed on silica gel H. ESI mass spectra analyses were completed on a Thermo Fisher Scientific LTQ FT Ultra mass spectrometer. *o*-Nitrobenzoic acid including its substituted derivatives and all solvents were obtained from commercial sources and were used as received or after drying and redistillation. All *o*-nitrobenzoic *N*-allylamides were prepared according to the literature. Chromatographic separation was performed on a silica gel H column using petroleum ether (PE)/ethyl acetate (EA) as a mobile phase. All reactions were carried out under a nitrogen atmosphere.

General Procedure A: Preparation of *N*-(Furan-2-ylmethyl)-2-nitrobenzamide³² (**1a**).

The preparation strategies of the other derivatives were consistent with its preparation strategy. *o*-Nitrobenzoic acid (500 mg, 2.99 mmol) was placed in a 250 mL clean anhydrous round-bottom flask under nitrogen atmosphere. Sulfoxide dichloride (4 mL) was added into the flask, and the mixture was stirred at 80 °C for 2 h. After completing the reaction, the redundant sulfoxide dichloride was removed under reduced pressure to obtain *o*-nitrobenzoyl chloride. Furamethylamine (0.32 mL, 3.3 mmol) was placed in another 250 mL dried round-bottom flask with stirring under anhydrous conditions and nitrogen atmosphere. Anhydrous CH₂Cl₂ (20 mL) and pyridine (3 mL) were injected into the flask by a syringe. Then, the prepared *o*-nitrobenzoyl chloride was added under an ice bath. After completing the above operation, the flask was placed at room temperature with stirring for 10 h. TLC plate monitored the end of the reaction, which was quenched by adding saturated sodium bicarbonate solution (50 mL) and extracted by using ethyl acetate (30 mL × 2), washed with saturated sodium chloride solution (50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Purification was done by column chromatography on silica gel H with petroleum ether/ethyl acetate (3:1) as eluent to give the pure white solid (664 mg).

***N*-(Furan-2-ylmethyl)-2-nitrobenzamide (**1a**, **1u**, **1w**).**—Prepared from *o*-nitrobenzoic acid (500 mg, 2.99 mmol) with furfurylamine (0.32 mL, 3.3 mmol) purified following general procedure A; afforded 664 mg (90% yield) of the title compound as a off-white solid; *R*_f = 0.32 (2:1 PE/EA), mp 108–109 °C; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.06 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.67 (td, *J* = 7.5, 1.3 Hz, 1H), 7.58 (td, *J* = 8.0, 1.6 Hz, 1H), 7.52 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.38 (t, *J* = 1.2 Hz, 1H), 6.35 (d, *J* = 1.2 Hz, 2H), 6.21 (s, 1H), 4.65 (d, *J* = 5.5 Hz, 2H); Literature data:³³ White solid; mp 108–110 °C; ¹H NMR (300 MHz, CDCl₃) δ 4.56 (2H, d, *J* = 5.7 Hz), 6.29 (1H, dd, *J* = 3.3 Hz, *J* = 0.9 Hz), 6.32 (1H, dd, *J* = 1.8 Hz, *J* = 3.3 Hz), 6.42 (1H, m, *J* = 5.7 Hz), 7.34 (1H, dd, *J* = 1.8 Hz, *J* = 0.9 Hz), 7.44–7.47 (1H, m), 7.50–7.56 (1H, m), 7.59–7.65 (1H, m), 7.98–8.01 (1H, m); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 37.1, 107.9, 110.5, 124.5, 128.7, 130.5, 132.4, 133.7, 142.3, 146.1, 150.3, 166.2.

3-Chloro-*N*-(furan-2-ylmethyl)-2-nitrobenzamide (1b**).**—Prepared from 3-chloro-2-nitrobenzoic acid (500 mg, 2.49 mmol) with furfurylamine (0.27 mL, 2.81 mmol) purified

following general procedure A; afforded 610 mg (87% yield) of the title compound as a white solid: R_f = 0.5 (2:1 PE/EA), mp 121–122 °C; ^1H NMR (600 MHz, Chloroform-*d*) δ 7.60 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.37 (s, 1H), 6.44 (s, 1H), 6.34 (d, J = 2.9 Hz, 1H), 6.30 (d, J = 2.9 Hz, 1H), 4.56 (d, J = 5.4 Hz, 2H).

N-(Furan-2-ylmethyl)-5-methyl-2-nitrobenzamide (1c).—Prepared from 5-methyl-2-nitrobenzoic acid (500 mg, 2.76 mmol) with furfurylamine (0.3 mL, 3.12 mmol) purified following general procedure A; afforded 665 mg (93% yield) of the title compound as a off-white solid: R_f = 0.3 (2:1 PE/EA); mp 135–137 °C; ^1H NMR (600 MHz, Chloroform-*d*) δ 7.97 (d, J = 8.3 Hz, 1H), 7.38 (s, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.29 (s, 1H), 6.35 (s, 2H), 6.18 (s, 1H), 4.63 (d, J = 5.4 Hz, 2H), 2.44 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, Chloroform-*d*) δ 166.6, 150.4, 145.4, 143.9, 142.4, 132.7, 130.9, 129.3, 124.7, 110.6, 108.0, 37.2, 21.4; HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{13}\text{O}_4\text{N}_2$, 261.0870; found, 261.0868.

N-(Furan-2-ylmethyl)-5-methoxy-2-nitrobenzamide (1d).—Prepared from 5-methoxy-2-nitrobenzoic acid (500 mg, 2.54 mmol) with furfurylamine (0.28 mL, 2.87 mmol) purified following general procedure A; afforded 668 mg (95% yield) of the title compound as a brown solid: R_f = 0.4 (2:1 PE/EA), mp 131–133 °C; ^1H NMR (600 MHz, Chloroform-*d*) δ 8.11 (d, J = 9.1 Hz, 1H), 7.37 (s, 1H), 6.97 (dd, J = 9.1, 1.8 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H), 6.35 (s, 2H), 6.15 (s, 1H), 4.64 (d, J = 5.4 Hz, 2H), 3.90 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, Chloroform-*d*) δ 166.4, 163.7, 150.3, 142.3, 138.7, 135.1, 127.1, 115.0, 113.9, 110.6, 108.0, 56.2, 37.2.

4-Fluoro-N-(furan-2-ylmethyl)-2-nitrobenzamide (1e).—Prepared from 4-fluoro-2-nitrobenzoic acid (500 mg, 2.70 mmol) with furfurylamine (0.38 mL, 3.05 mmol) purified following general procedure A; afforded 509 mg (71% yield) of the title compound as a white solid: R_f = 0.38 (2:1 PE/EA), mp 115–117 °C; ^1H NMR (600 MHz, DMSO-*d*₆) δ 9.20 (t, J = 5.7 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 5.7 Hz, 2H), 7.61 (s, 1H), 6.43 (s, 1H), 6.34 (s, 1H), 4.43 (d, J = 5.5 Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, DMSO-*d*₆) δ 164.8, 162.1 (d, J = 249.0 Hz), 151.9, 148.7 (d, J = 9.0 Hz), 142.7, 131.7 (d, J = 9.0 Hz), 128.8 (d, J = 3.0 Hz), 120.8 (d, J = 22.5 Hz), 112.5 (d, J = 27.0 Hz), 111.0, 107.5, 36.6; HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{10}\text{O}_4\text{N}_2\text{F}$, 265.0619; found, 265.0626.

2-Nitro-N-(thiophen-2-ylmethyl)benzamide (1f).—Prepared from 2-nitrobenzoic acid (500 mg, 2.99 mmol) with thiophen-2-ylmethanamine (0.4 mL, 3.4 mmol) purified following general procedure A; afforded 670 mg (86% yield) of the title compound as a off-white solid: R_f = 0.3 (2:1 PE/EA), mp 117–119 °C; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.05 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 7.4 Hz, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.25 (d, J = 4.3 Hz, 1H), 7.07 (d, J = 3.0 Hz, 1H), 6.98 (dd, J = 4.8, 3.6 Hz, 1H), 6.24 (s, 1H), 4.81 (d, J = 5.6 Hz, 2H).

3-Chloro-2-nitro-N-(thiophen-2-ylmethyl)benzamide (1g).—Prepared from 3-chloro-2-nitrobenzoic acid (500 mg, 2.49 mmol) with thiophen-2-ylmethanamine (0.33 mL, 2.81 mmol) purified following general procedure A; afforded 672 mg (91% yield) of the title compound as a off-white solid: R_f = 0.28 (2:1 PE/EA), mp 164–165 °C; ^1H NMR (400

MHz, Chloroform-*d*) δ 7.59 (dd, J = 7.7, 1.0 Hz, 1H), 7.44–7.51 (m, 2H), 7.25 (d, J = 1.7 Hz, 1H), 7.02 (d, J = 1.7 Hz, 1H), 6.96 (t, J = 4.2 Hz, 1H), 6.38 (s, 1H), 4.73 (d, J = 5.6 Hz, 2H).

5-Methyl-2-nitro-N-(thiophen-2-ylmethyl)benzamide (1h).—Prepared from 5-methyl-2-nitrobenzoic acid (500 mg, 2.76 mmol) with thiophen-2-ylmethanamine (0.37 mL, 3.12 mmol) purified following general procedure A; afforded 668 mg (88% yield) of the title compound as a brown solid: R_f = 0.32 (2:1 PE/EA), mp 138–139 °C; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.96 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 1.1 Hz, 1H), 7.25 (dd, J = 5.1, 1.2 Hz, 1H), 7.06 (d, J = 2.9 Hz, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.23 (s, 1H), 4.79 (d, J = 5.6 Hz, 2H), 2.44 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, Chloroform-*d*) δ 166.4, 145.4, 143.8, 139.8, 132.6, 130.8, 129.2, 127.0, 126.5, 125.5, 124.6, 38.8, 21.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{13}\text{O}_3\text{N}_2\text{S}$, 277.0641; found, 277.0639.

3-Methyl-2-nitro-N-(thiophen-2-ylmethyl)benzamide (1i).—Prepared from 3-methyl-2-nitrobenzoic acid (500 mg, 2.76 mmol) with thiophen-2-ylmethanamine (0.37 mL, 3.12 mmol) purified following general procedure A; afforded 679 mg (89% yield) of the title compound as a white solid: R_f = 0.3 (2:1 PE/EA), mp 135–136 °C; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.40 (s, 3H), 7.24 (d, J = 4.7 Hz, 1H), 7.03 (d, J = 3.0 Hz, 1H), 6.96 (dd, J = 4.7, 3.6 Hz, 1H), 6.41 (s, 1H), 4.73 (d, J = 5.6 Hz, 2H), 2.37 (s, 3H).

2-Nitro-N-(2-(pyridin-2-yl)ethyl)benzamide (1j).—Prepared from 2-nitrobenzoic acid (500 mg, 2.99 mmol) with 2-(pyridin-2-yl)ethan-1-amine (0.42 mL, 3.4 mmol) purified following general procedure A; afforded 720 mg (89% yield) of the title compound as a yellow solid: R_f = 0.56 (EA), mp 102–103 °C; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.43 (dd, J = 4.5, 0.4 Hz, 1H), 8.00 (dd, J = 8.1, 0.8 Hz, 1H), 7.64 (td, J = 7.6, 1.6 Hz, 2H), 7.54 (td, J = 8.0, 1.4 Hz, 1H), 7.49 (dd, J = 7.5, 1.4 Hz, 1H), 7.27–7.24 (m, 1H), 7.22 (s, 1H), 7.17–7.12 (m, 1H), 3.87 (q, J = 6.0 Hz, 2H), 3.12 (t, J = 6.2 Hz, 2H).

2-Nitro-N-(2-(thiophen-2-yl)ethyl)benzamide (1k).—Prepared from 2-nitrobenzoic acid (500 mg, 2.99 mmol) with 2-(thiophen-2-yl)ethan-1-amine (0.44 mL, 3.4 mmol) purified following general procedure A; afforded 740 mg (90% yield) of the title compound as a yellow waxy solid: R_f = 0.3 (2:1 PE/EA); mp 88–90 °C; ^1H NMR (600 MHz, Chloroform-*d*) δ 8.04 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.16 (d, J = 4.8 Hz, 1H), 6.94 (d, J = 4.5 Hz, 1H), 6.91 (s, 1H), 5.99 (s, 1H), 3.74 (q, J = 6.2 Hz, 2H), 3.19 (t, J = 6.4 Hz, 2H).

2-Chloro-2-nitro-N-(2-(thiophen-2-yl)ethyl)benzamide (1l).—Prepared from 3-chloro-2-nitrobenzoic acid (500 mg, 2.49 mmol) with 2-(thiophen-2-yl)ethan-1-amine (0.36 mL, 2.81 mmol) purified following general procedure A; afforded 698 mg (90% yield) of the title compound as a yellow solid: R_f = 0.3 (2:1 PE/EA), mp 134–136 °C; ^1H NMR (600 MHz, Chloroform-*d*) δ 7.59 (d, J = 7.8 Hz, 1H), 7.48–7.43 (m, 2H), 7.18 (d, J = 5.0 Hz, 1H), 6.97 (t, J = 4.1 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.18 (s, 1H), 3.67 (q, J = 6.3 Hz, 2H), 3.13 (t, J = 6.5 Hz, 2H).

5-Methyl-2-nitro-N-(2-(thiophen-2-yl)ethyl)benzamide (1m).—Prepared from 5-methyl-2-nitrobenzoic acid (500 mg, 2.76 mmol) with 2-(thiophen-2-yl)ethan-1-amine (0.4 mL, 3.12 mmol) purified following general procedure A; afforded 705 mg (88% yield) of the title compound as a off-white solid: R_f = 0.33 (2:1 PE/EA); mp 100–102 °C; ^1H NMR (600 MHz, Chloroform-*d*) δ 7.96 (d, J = 8.3 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.22 (s, 1H), 7.16 (d, J = 4.8 Hz, 1H), 6.95 (t, J = 4.8 Hz, 1H), 6.91 (s, 1H), 5.99 (s, 1H), 3.73 (q, J = 6.4 Hz, 2H), 3.18 (t, J = 6.4 Hz, 2H), 2.43 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, Chloroform-*d*) δ 166.9, 145.3, 143.8, 141.0, 132.9, 130.7, 129.1, 127.1, 125.6, 124.6, 123.9, 41.3, 29.5, 21.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{15}\text{O}_3\text{N}_2\text{S}$, 291.0798; found, 291.0794.

N-Benzyl-2-nitrobenzamide (1n).—Prepared from 2-nitrobenzoic acid (500 mg, 2.99 mmol) with phenylmethanamine (0.37 mL, 3.4 mmol) purified following general procedure A; afforded 637 mg (83% yield) of the title compound as a off-white solid: R_f = 0.38 (2:1 PE/EA), mp 123–124 °C; ^1H NMR (600 MHz, Chloroform-*d*) δ 8.04 (d, J = 8.1 Hz, 1H), 7.65 (td, J = 7.8, 0.4 Hz, 1H), 7.56 (td, J = 7.5, 0.7 Hz, 1H), 7.51 (dd, J = 7.5, 0.6 Hz, 1H), 7.39–7.34 (m, 4H), 7.31–7.29 (m, 1H), 6.20 (s, 1H), 4.62 (d, J = 5.6 Hz, 2H). Literature data:³⁴ Light brown solid; mp 121–122 °C; ^1H NMR (300 MHz, CDCl_3) δ 9.21 (t, J = 5.7 Hz, 1H), 8.04 (dd, J = 7.9, 1.0 Hz, 1H), 7.80 (td, J = 7.4, 1.1 Hz, 1H), 7.72–7.64 (m, 2H), 7.36 (m, 4H), 7.27 (m, 1H), 4.46 (d, J = 6.0 Hz, 2H).

N-Benzyl-3-methyl-2-nitrobenzamide (1o, 1a₁).—Prepared from 3-methyl-2-nitrobenzoic acid (500 mg, 2.76 mmol) with phenylmethanamine (0.34 mL, 3.12 mmol) purified following general procedure A; afforded 680 mg (91% yield) of the title compound as a off-white solid: R_f = 0.3 (3:1 PE/EA), mp 137–138 °C; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.42–7.27 (m, 8H), 6.31 (s, 1H), 4.57 (d, J = 5.7 Hz, 2H), 2.38 (s, 3H).

N-(2,6-Dimethylbenzyl)-3-methyl-2-nitrobenzamide (1p, 1v).—Prepared from 3-methyl-2-nitrobenzoic acid (500 mg, 2.76 mmol) with (2,6-dimethylphenyl)methanamine (0.43 mL, 3.12 mmol) purified following general procedure A; afforded 734 mg (89% yield) of the title compound as a white solid: R_f = 0.3 (3:1 PE/EA), mp 153–154 °C; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.40–7.33 (m, 3H), 7.16–7.12 (m, 1H), 7.07 (d, J = 7.4 Hz, 2H), 5.78 (s, 1H), 4.62 (d, J = 4.6 Hz, 2H), 2.41 (s, 6H), 2.37 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, Chloroform-*d*) δ 165.1, 149.2, 137.7, 133.5, 133.1, 131.0, 130.4, 129.9, 128.4, 128.0, 125.8, 38.8, 19.6, 17.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{19}\text{O}_3\text{N}_2$, 299.1390; found, 299.1394.

N-3-Dimethyl-2-nitrobenzamide (1q).—Prepared from 3-methyl-2-nitrobenzoic acid (542 mg, 2.99 mmol) with iodomethane (0.49 mL, 3.4 mmol) purified following general procedure A; afforded 478 mg (82% yield) of the title compound as a yellow solid: R_f = 0.12 (3:1 PE/EA), mp 133–135 °C; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.43–7.36 (m, 3H), 6.18 (s, 1H), 2.93 (d, J = 4.8 Hz, 3H), 2.36 (s, 3H).

N-(4-Fluorophenethyl)-2-nitrobenzamide (1r).—Prepared from 2-nitrobenzoic acid (500 mg, 2.99 mmol) with 2-(4-fluorophenyl)-ethan-1-amine (0.48 mL, 3.4 mmol) purified following general procedure A; afforded 795 mg (92% yield) of the title compound as a off-white solid: R_f = 0.33 (2:1 PE/EA), mp 103–104 °C; ^1H NMR (400 MHz, Chloroform-*d*)

δ 8.04 (dd, J = 8.0, 1.2 Hz, 1H), 7.64 (td, J = 7.5, 1.2 Hz, 1H), 7.55 (td, J = 8.0, 1.5 Hz, 1H), 7.41 (dd, J = 7.4, 1.5 Hz, 1H), 7.24–7.20 (m, 2H), 7.02–6.97 (m, 2H), 5.88 (s, 1H), 3.70 (q, J = 6.9 Hz, 2H), 2.94 (t, J = 6.9 Hz, 2H).

N-(4-Fluorophenethyl)-5-methyl-2-nitrobenzamide (1s).—Prepared from 5-methyl-2-nitrobenzoic acid (500 mg, 2.76 mmol) with 2-(4-fluorophenyl)ethan-1-amine (0.44 mL, 3.12 mmol) purified following general procedure A; afforded 778 mg (93% yield) of the title compound as a brown solid: R_f = 0.35 (3:1 PE/EA), mp 125–127 °C; ^1H NMR (400 MHz, Chloroform- d) δ 8.69 (t, J = 4.4 Hz, 1H), 7.94 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.34–7.26 (m, 3H), 7.13 (t, J = 8.8 Hz, 2H), 3.43 (q, J = 6.8 Hz, 2H), 2.82 (t, J = 7.2 Hz, 2H), 2.41 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, DMSO- d_6) δ 166.0, 161.3 (d, J = 241.5 Hz), 144.9, 135.8 (d, J = 3 Hz), 133.3, 131.0, 130.9 (d, J = 7.5 Hz), 130.3, 129.7, 124.5, 115.4 (d, J = 21.0 Hz), 41.0, 34.2, 21.1.

N-(4-Fluorophenethyl)-3-methyl-2-nitrobenzamide (1t).—Prepared from 3-methyl-2-nitrobenzoic acid (542 mg, 2.99 mmol) with 2-(4-fluorophenyl)ethan-1-amine (0.48 mL, 3.4 mmol) purified following general procedure A; afforded 802 mg (89% yield) of the title compound as a off-white solid: R_f = 0.35 (3:1 PE/EA), mp 105–106 °C; ^1H NMR (400 MHz, Chloroform- d) δ 8.82 (t, J = 5.3 Hz, 1H), 7.56 (d, J = 5.2 Hz, 2H), 7.48–7.41 (m, 1H), 7.28 (dd, J = 8.3, 5.8 Hz, 2H), 7.12 (t, J = 8.8 Hz, 2H), 3.41 (q, J = 6.9 Hz, 2H), 2.80 (t, J = 7.1 Hz, 2H), 2.29 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, DMSO- d_6) δ 164.6, 161.1 (d, J = 240.1 Hz), 149.2, 135.6 (d, J = 2.1 Hz), 133.7, 130.7 (d, J = 4.2 Hz), 130.6, 130.4, 129.9, 126.3, 115.2 (d, J = 20.9 Hz), 40.9, 34.0, 17.0.

N-(4-Methoxyphenyl)-2-nitrobenzamide (1x).—Prepared from 2-nitrobenzoic acid (500 mg, 2.99 mmol) with 4-methoxyaniline (0.42 mL, 3.4 mmol) purified following general procedure A; afforded 787 mg (97% yield) of the title compound as a off-white solid: R_f = 0.46 (2:1 PE/EA), mp 169–170 °C; ^1H NMR (400 MHz, Chloroform- d) δ 10.54 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.86 (t, J = 7.5 Hz, 1H), 7.78–7.72 (m, 2H), 7.59 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 3.75 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform- d) δ 163.8, 155.9, 146.8, 134.2, 133.0, 132.2, 131.1, 129.5, 124.4, 121.4, 114.1, 55.4. Literature data:³⁵ yellow needles; mp 168–169 °C.

2-Nitro-N-(*m*-tolyl)benzamide (1y).—Prepared from 2-nitrobenzoic acid (500 mg, 2.99 mmol) with *m*-toluidine (0.37 mL, 3.4 mmol) purified following general procedure A; afforded 652 mg (85% yield) of the title compound as a brown solid: R_f = 0.16 (3:1 PE/EA); mp 141–143 °C; ^1H NMR (400 MHz, Chloroform- d) δ 8.07 (d, J = 8.1 Hz, 1H), 7.72–7.58 (m, 3H), 7.44 (s, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 6.99 (m, 1H), 6.63–6.50 (m, 1H), 2.35 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform- d) δ 164.5, 139.0, 137.2, 133.8, 132.8, 130.5, 128.8, 128.5, 125.9, 124.5, 121.1, 119.7, 117.5, 21.4. Literature data:³⁶ mp 145–147 °C.

2-Nitro-N-phenylbenzamide (1z).—Prepared from 2-nitrobenzoic acid (200 mg, 1.2 mmol) with aniline (0.13 mL, 1.35 mmol) purified following general procedure A; afforded 236 mg (81% yield) of the title compound as a brown solid: R_f = 0.52 (1:1 PE/EA), mp

154–156 °C; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.10 (d, J = 8.0 Hz, 1H), 7.73–7.56 (m, 6H), 7.37 (t, J = 7.7 Hz, 2H), 7.19 (t, J = 7.3 Hz, 1H).

General Procedure B: Synthesis of *N*-(Furan-2-ylmethyl)-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide¹⁸ (1aa).

N-(Furan-2-ylmethyl)-2-nitrobenzamide (246 mg, 1 mmol) (**1a**) was placed in a 100 mL clean anhydrous round-bottom flask under nitrogen atmosphere, and anhydrous THF (15 mL) was injected by a 20 mL syringe. Then, the flask was placed in an ice bath, and LDA (ca. 2.0 M, 0.75 mL, 1.5 mmol) was added with stirring for 15 min. 3,3-Dimethylallyl bromide (220 mg, 1.5 mmol) was slowly dripped into the flask by a 1 mL syringe. After 3 h, the reaction was monitored by TLC plate and quenched by adding saturated ammonium chloride solution (40 mL), extracted with ethyl acetate (25 mL $\times$ 2), washed with saturated sodium chloride solution (20 mL $\times$ 2), dried over Na_2SO_4 , and concentrated under reduced pressure. Purification was done by column chromatography on silica gel H with petroleum ether/ethyl acetate (4:1) as eluent to give the light yellow oily liquid (266.9 mg). The synthesis process of these compounds used the same method, and the polarity of the products is also similar, all belonging to oily substances. Compound **1pp** and **1zz** were identified by $^1\text{H}/^{13}\text{C}$ NMR and HMRS. The reaction solutions of the rest of the compounds were separated by rapid chromatographic column and went directly into the general procedure C.

***N*-(2,6-Dimethylbenzyl)-3-methyl-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide (1pp).**—Prepared from *N*-(2,6-dimethylbenzyl)-3-methyl-2-nitrobenzamide (150 mg, 0.503 mmol) (**1p**) and purified following general procedure B; afforded 116 mg (63% yield) of the title compound as a yellow oil: R_f = 0.4 (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.45–7.37 (m, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.14–7.08 (m, 1H), 7.06–7.00 (m, 2H), 5.10 (t, J = 7.5 Hz, 1H), 4.89 (s, 2H), 3.56 (d, J = 6.0 Hz, 2H), 2.46 (s, 3H), 2.36 (s, 6H), 1.60 (s, 3H), 0.96 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform-*d*) δ 167.4, 148.0, 138.5, 135.8, 132.4, 132.3, 132.2, 131.8, 131.0, 128.5, 127.8, 125.3, 120.3, 45.3, 42.5, 25.7, 20.0, 19.0, 17.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{26}\text{O}_3\text{N}_2\text{Na}$, 389.1836; found, 389.1839.

***N*-(3-Methylbut-2-en-1-yl)-2-nitro-*N*-phenylbenzamide (1zz).**—Prepared from 2-nitro-*N*-phenylbenzamide (123 mg, 0.52 mmol) (**1z**) and purified following general procedure B; afforded 112.8 mg (70% yield) of the title compound as a yellow waxy solid: R_f = 0.4 (2:1 PE/EA), 62–64 °C; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.90 (d, J = 8.2 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.8 Hz, 2H), 7.19–6.98 (m, 5H), 5.41 (t, J = 7.0 Hz, 1H), 4.54 (d, J = 7.1 Hz, 2H), 1.71 (s, 3H), 1.51 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform-*d*) δ 166.6, 145.7, 141.5, 136.9, 133.5, 133.4, 129.4, 129.3, 129.1, 128.2, 127.7, 124.2, 118.6, 47.2, 25.7, 17.8; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{19}\text{O}_3\text{N}_2$, 311.1390; found, 311.1391.

General Procedure C.

4-(Furan-2-ylmethyl)-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5*H*-benzo[e][1,4]diazepin-5-one **2a** was used as the model product for this reaction. The preparation strategies of the

other diazepines were consistent with its preparation strategy. *N*-(Furan-2-ylmethyl)-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide **1aa** (30 mg, 0.096 mmol) was placed in a 15 mL test tube with an agitator, and triphenylphosphine (63 mg, 0.24 mmol), molybdenum-acetoacetate (3.1 mg, 0.0096 mmol), and copper(II) trifluoro-methane-sulfonate (3.5 mg, 0.0096 mmol) were added successively. After that, dried toluene (3 mL) was added into the test tube. Then, the test tube was placed in an oil bath at 110 °C for 12 h. The whole operation process was carried out without water and oxygen under N₂ atmosphere rigidly. The TLC plate was used for monitoring the end of the reaction. The mixture was diluted with ethyl acetate (10 mL) and washed with saturated sodium chloride solution (15 mL × 2), dried over Na₂SO₄, and concentrated under reduced pressure. Purification was done by column chromatography on silica gel H with petroleum ether/ethyl acetate (4:1, v/v) as eluent to give **2a** as a white solid (24.4 mg).

4-(Furan-2-ylmethyl)-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e]

[1,4]diazepin-5-one (2a).—Prepared from *N*-(furan-2-ylmethyl)-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide (30 mg, 0.096 mmol) and purified following the procedure C; afforded 24.4 mg (90% yield) of the product as a white solid: *R*_f = 0.45 (2:1 PE/EA), mp 120–122 °C; ¹H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 7.7 Hz, 1H), 7.37 (s, 1H), 7.26 (t, *J* = 7.6 Hz, 2H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.34 (s, 1H), 5.02 (s, 2H), 4.96 (d, *J* = 15.5 Hz, 2H), 4.53 (d, *J* = 15.4 Hz, 1H), 4.03 (dd, *J* = 8.8, 3.1 Hz, 1H), 3.54 (dd, *J* = 15.2, 8.8 Hz, 1H), 3.41 (dd, *J* = 15.2, 3.1 Hz, 1H), 1.73 (s, 3H); ¹³C{¹H} NMR (100 MHz, Chloroform-*d*) δ 169.6, 150.8, 145.4, 144.4, 142.4, 132.4, 132.1, 122.5, 119.6, 119.2, 113.0, 110.6, 109.0, 65.3, 48.6, 43.8, 19.4; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₇H₁₉N₂O₂, 283.1441; found, 283.1440. Larger scale synthesis: Prepared from *N*-(furan-2-ylmethyl)-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide (387 mg, 1.23 mmol) and purified following the procedure C; afforded 208.4 mg (60% yield) of **2a**.

9-Chloro-4-(furan-2-ylmethyl)-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e]

[1,4]diazepin-5-one (2b).—Prepared from 3-chloro-*N*-(furan-2-ylmethyl)-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide (36 mg, 0.103 mmol) and purified following the procedure C; afforded 19.6 mg (60% yield) of the product as a light yellow oil: *R*_f = 0.42 (2:1 PE/EA); ¹H NMR (400 MHz, Chloroform-*d*) δ 7.73 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.46–7.35 (m, 2H), 6.77 (t, *J* = 7.8 Hz, 1H), 6.36 (s, 2H), 5.13 (s, 1H), 5.12 (d, *J* = 15.3 Hz, 1H), 4.96 (s, 1H), 4.59 (s, 1H), 4.43 (d, *J* = 15.3 Hz, 1H), 4.00 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.59 (dd, *J* = 15.2, 8.4 Hz, 1H), 3.42 (dd, *J* = 15.2, 2.7 Hz, 1H), 1.73 (s, 3H); ¹³C{¹H} NMR (100 MHz, Chloroform-*d*) δ 168.6, 150.4, 144.5, 142.5, 140.5, 132.2, 131.2, 123.2, 122.4, 118.8, 113.6, 110.6, 109.2, 65.2, 48.6, 43.9, 19.0; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₇H₁₈N₂O₂Cl, 317.1051; found, 317.1048.

4-(Furan-2-ylmethyl)-7-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-

benzo[e][1,4]diazepin-5-one (2c).—Prepared from *N*-(furan-2-ylmethyl)-5-methyl-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide (29 mg, 0.09 mmol) and purified following the procedure C; afforded 21.7 mg (83% yield) of the product as a light yellow oil: *R*_f = 0.56 (2:1 PE/EA); ¹H NMR (400 MHz, Chloroform-*d*) δ 7.61 (s, 1H), 7.40 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.37 (s, 2H), 5.09 (d, *J* = 15.3 Hz, 1H), 5.08 (s, 1H),

4.92 (s, 1H), 4.48 (d, $J = 15.3$ Hz, 1H), 3.96 (dd, $J = 8.4, 3.1$ Hz, 1H), 3.58 (dd, $J = 15.1, 8.4$ Hz, 1H), 3.42 (dd, $J = 15.0, 3.1$ Hz, 1H), 2.29 (s, 3H), 1.73 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform- d) δ 169.8, 150.8, 145.7, 142.3, 142.2, 133.2, 131.8, 129.0, 122.7, 119.3, 112.7, 110.5, 108.9, 65.4, 48.6, 43.7, 20.2, 19.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_2$, 297.1598; found, 297.1596.

4-(Furan-2-ylmethyl)-7-methoxy-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2d).—Prepared from *N*-(furan-2-ylmethyl)-5-

methoxy-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide (150 mg, 0.44 mmol) and purified following the procedure C; afforded 111.3 mg (81% yield) of the product as a light yellow oil: $R_f = 0.5$ (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform- d) δ 7.39 (s, 1H), 7.32 (d, $J = 3.0$ Hz, 1H), 6.87 (dd, $J = 8.7, 3.0$ Hz, 1H), 6.62 (d, $J = 8.7$ Hz, 1H), 6.35 (s, 2H), 5.08 (d, $J = 15.3$ Hz, 1H), 5.04 (s, 1H), 4.90 (s, 1H), 4.47 (d, $J = 15.3$ Hz, 1H), 3.94 (dd, $J = 8.3, 3.4$ Hz, 1H), 3.88 (s, 1H), 3.79 (s, 3H), 3.55 (dd, $J = 15.1, 8.3$ Hz, 1H), 3.40 (dd, $J = 15.1, 3.5$ Hz, 1H), 1.71 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform- d) δ 169.5, 153.4, 150.7, 145.6, 142.3, 138.4, 124.1, 121.0, 120.3, 114.2, 112.6, 110.5, 108.8, 65.5, 55.6, 48.5, 43.7, 19.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_3$, 313.1547; found, 313.1546. Larger scale synthesis: prepared from *N*-(furan-2-ylmethyl)-5-methoxy-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide (301 mg, 0.88 mmol) and purified following the procedure C; afforded 174.9 mg (64% yield) of **2d**.

8-Fluoro-4-(furan-2-ylmethyl)-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2e).—Prepared from 4-fluoro-*N*-(furan-2-ylmethyl)-*N*-(3-

methylbut-2-en-1-yl)-2-nitrobenzamide (140 mg, 0.42 mmol) and purified following the procedure C; afforded 65.5 mg (52% yield) of the product as a light yellow oil: $R_f = 0.6$ (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform- d) δ 7.83 (dd, $J = 8.7, 6.9$ Hz, 1H), 7.39 (s, 1H), 6.55 (td, $J = 8.6, 2.3$ Hz, 1H), 6.35–6.34 (m, 2H), 6.32 (d, $J = 2.3$ Hz, 1H), 5.11 (d, $J = 15.3$ Hz, 1H), 5.03 (s, 1H), 4.94 (s, 1H), 4.40 (d, $J = 15.3$ Hz, 1H), 3.91 (dd, $J = 8.3, 2.2$ Hz, 1H), 3.90 (s, 1H), 3.58 (dd, $J = 15.1, 8.3$ Hz, 1H), 3.43 (dd, $J = 15.1, 2.2$ Hz, 1H), 1.72 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform- d) δ 168.7, 165.4 (d, $J = 249.0$ Hz), 150.6, 146.5 (d, $J = 11.0$ Hz), 145.1, 142.5, 135.0 (d, $J = 10.0$ Hz), 118.0 (d, $J = 2.0$ Hz), 113.2, 110.6, 109.1, 106.8 (d, $J = 22.0$ Hz), 104.7 (d, $J = 24.0$ Hz), 65.0, 48.7, 43.9, 19.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{17}\text{FNaO}_2$, 323.1166; found, 323.1169.

2-(Prop-1-en-2-yl)-4-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2f).—Prepared from *N*-(3-methylbut-2-en-1-yl)-2-nitro-*N*-(thiophen-2-ylmethyl)benzamide (39 mg, 0.118 mmol) and purified following the

procedure C; afforded 22.9 mg (65% yield) of the product as a light yellow oil: $R_f = 0.6$ (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform- d) δ 7.83 (dd, $J = 7.6, 0.9$ Hz, 1H), 7.26–7.22 (m, 2H), 7.03 (d, $J = 3.1$ Hz, 1H), 6.95 (dd, $J = 4.9, 3.6$ Hz, 1H), 6.90 (t, $J = 7.5$ Hz, 1H), 6.70 (d, $J = 8.0$ Hz, 1H), 5.14 (d, $J = 15.1$ Hz, 1H), 5.05 (s, 1H), 4.92 (s, 1H), 4.68 (d, $J = 15.1$ Hz, 1H), 4.02 (dd, $J = 8.3, 3.1$ Hz, 1H), 3.52 (dd, $J = 15.1, 8.3$ Hz, 1H), 3.37 (dd, $J = 15.1, 3.1$ Hz, 1H), 1.70 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform- d) δ 169.6, 145.2, 144.5, 139.7, 132.5, 132.1, 127.0, 126.7, 125.8, 122.3, 119.6, 119.2, 113.2, 65.4, 48.5, 46.1, 19.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{OS}$, 299.1213; found, 299.1211.

9-Chloro-2-(prop-1-en-2-yl)-4-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2g).

—Prepared from 3-chloro-*N*-(3-methylbut-2-en-1-yl)-2-nitro-*N*-(thiophen-2-ylmethyl)-benzamide (35 mg, 0.096 mmol) and purified following the procedure C; afforded 18.8 mg (59% yield)

of the product as a light yellow oil: $R_f = 0.4$ (2:1 PE/

EA); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.76 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.41 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.28 (s, 1H), 7.05 (d, $J = 2.9$ Hz, 1H), 6.97 (dd, $J = 4.9, 3.6$ Hz, 1H), 6.79 (t, $J = 7.8$ Hz, 1H), 5.20 (d, $J = 15.1$ Hz, 1H), 5.12 (s, 1H), 4.96 (s, 1H), 4.66 (d, $J = 15.1$ Hz, 1H), 4.06 (dd, $J = 8.2, 2.7$ Hz, 1H), 3.56 (dd, $J = 15.2, 8.2$ Hz, 1H), 3.38 (dd, $J = 15.2, 2.7$ Hz, 1H), 1.72 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform-*d*) δ 167.5, 143.3, 139.5, 138.2, 131.2, 130.2, 126.1, 125.7, 124.9, 122.3, 121.4, 117.9, 112.7, 64.3, 47.5, 45.2, 17.9; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{OClS}$, 333.0823; found, 333.0820.

7-Methyl-2-(prop-1-en-2-yl)-4-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2h).

—Prepared from 5-methyl-*N*-(3-methylbut-2-en-1-yl)-2-nitro-*N*-(thiophen-2-ylmethyl)-benzamide (36 mg, 0.105 mmol) and purified following the procedure C; afforded 20.9 mg (64% yield) of the product

as a light yellow oil: $R_f = 0.5$ (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.62 (s, 1H), 7.25 (d, $J = 8.1$ Hz, 1H), 7.07–7.03 (m, 2H), 6.96 (t, $J = 8.1$ Hz, 1H), 6.58 (d, $J = 8.1$ Hz, 1H), 5.13 (d, $J = 15.1$ Hz, 1H), 5.08 (s, 1H), 4.91 (s, 1H), 4.68 (d, $J = 15.1$ Hz, 1H), 4.00 (dd, $J = 8.2, 3.2$ Hz, 1H), 3.52 (dd, $J = 15.1, 8.2$ Hz, 1H), 3.36 (dd, $J = 15.1, 3.2$ Hz, 1H), 2.28 (s, 3H), 1.70 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform-*d*) δ 169.8, 145.5, 142.2, 139.8, 133.3, 131.8, 129.1, 126.8, 126.6, 125.7, 122.7, 119.4, 112.9, 65.5, 48.5, 46.0, 20.3, 19.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{OS}$, 313.1369; found, 313.1367.

9-Methyl-2-(prop-1-en-2-yl)-4-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2i).

—Prepared from 3-methyl-*N*-(3-methylbut-2-en-1-yl)-2-nitro-*N*-(thiophen-2-ylmethyl)-benzamide (31 mg, 0.09 mmol) and purified following the procedure C; afforded 19.1 mg (68% yield)

of the product as a light yellow oil: $R_f = 0.5$ (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.71 (dd, $J = 7.8, 0.8$ Hz, 1H), 7.25 (dd, $J = 5.1, 0.8$ Hz, 1H), 7.18 (d, $J = 7.2$ Hz, 1H), 7.03 (d, $J = 2.9$ Hz, 1H), 6.96 (dd, $J = 5.0, 3.5$ Hz, 1H), 6.79 (t, $J = 7.6$ Hz, 1H), 5.23 (d, $J = 15.1$ Hz, 1H), 5.10 (s, 1H), 4.94 (s, 1H), 4.61 (d, $J = 15.1$ Hz, 1H), 4.02 (dd, $J = 7.6, 2.9$ Hz, 1H), 3.68 (s, 1H), 3.57 (dd, $J = 15.1, 7.6$ Hz, 1H), 3.37 (dd, $J = 15.1, 2.9$ Hz, 1H), 2.19 (s, 3H), 1.71 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, Chloroform-*d*) δ 169.9, 145.1, 142.5, 139.8, 133.4, 130.3, 126.9, 126.6, 125.7, 124.7, 122.6, 118.9, 113.3, 65.2, 48.5, 46.2, 19.1, 18.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{OS}$, 313.1369; found, 313.1368.

2-(Prop-1-en-2-yl)-4-(2-(pyridin-2-yl)ethyl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2j).

—Prepared from *N*-(3-methylbut-2-en-1-yl)-2-nitro-*N*-(2-(pyridin-2-yl)ethyl)benzamide (49 mg, 0.14 mmol) and purified following the procedure C; afforded 27.9 mg (63% yield) of the product as

a light yellow oil: $R_f = 0.6$ (EA); ^1H NMR (400 MHz, Chloroform-*d*) δ 8.55 (d, $J = 4.9$ Hz, 1H), 7.76 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.63 (td, $J = 7.6, 1.6$ Hz, 1H), 7.29 (s, 1H), 7.23 (td, $J = 7.6, 1.6$ Hz, 1H), 7.16 (t, $J = 5.0$ Hz, 1H), 6.87 (td, $J = 7.5, 1.0$ Hz, 1H), 6.63 (d, $J = 8.0$ Hz,

1H), 5.05 (s, 1H), 4.90 (s, 1H), 4.05–4.02 (m, 1H), 3.99 (dd, $J = 8.3, 3.1$ Hz, 1H), 3.88–3.81 (m, 1H), 3.48 (dd, $J = 15.0, 8.3$ Hz, 1H), 3.29 (dd, $J = 15.0, 3.1$ Hz, 1H), 3.24–3.10 (m, 2H), 1.71 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform- d) δ 168.8, 158.1, 148.1, 144.4, 143.6, 135.8, 131.2, 130.7, 123.0, 122.0, 120.6, 118.6, 118.1, 112.1, 64.8, 49.2, 48.3, 35.7, 18.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{22}\text{N}_3\text{O}$, 308.1757; found, 308.1755.

2-(Prop-1-en-2-yl)-4-(2-(thiophen-2-yl)ethyl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2k).—Prepared from *N*-(3-methylbut-2-en-1-yl)-2-nitro-*N*-(2-

(thiophen-2-yl)ethyl)benzamide (42 mg, 0.12 mmol) and purified following the procedure C; afforded 31.6 mg (83% yield) of the product as a light yellow oil: $R_f = 0.48$ (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform- d) δ 7.78 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.24 (dd, $J = 7.2, 1.3$ Hz, 1H), 7.16 (d, $J = 5.1$ Hz, 1H), 6.95–6.87 (m, 3H), 6.67 (d, $J = 8.0$ Hz, 1H), 5.08 (s, 1H), 4.93 (s, 1H), 3.99 (dd, $J = 8.1, 2.8$ Hz, 1H), 3.96–3.88 (m, 1H), 3.70–3.63 (m, 1H), 3.46 (dd, $J = 15.1, 8.1$ Hz, 1H), 3.30–3.13 (m, 2H), 3.25 (dd, $J = 15.1, 2.8$ Hz, 1H), 1.72 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform- d) δ 168.7, 144.2, 143.6, 140.6, 131.3, 130.7, 126.0, 124.5, 122.8, 122.0, 118.6, 118.1, 112.2, 64.7, 50.5, 49.5, 27.6, 18.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{OS}$, 313.1369; found, 313.1367.

9-Chloro-2-(prop-1-en-2-yl)-4-(2-(thiophen-2-yl)ethyl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2l).—Prepared from 3-chloro-*N*-(3-methylbut-2-en-1-

yl)-2-nitro-*N*-(2-(thiophen-2-yl)ethyl)benzamide (51 mg, 0.135 mmol) and purified following the procedure C; afforded 24.8 mg (53% yield) of the product as a light yellow oil: $R_f = 0.42$ (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform- d) δ 7.70 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.40 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.17 (dd, $J = 5.0, 0.8$ Hz, 1H), 6.98–6.92 (dd, $J = 5.0, 3.0$ Hz, 1H), 6.88 (d, $J = 3.0$ Hz, 1H), 6.79 (t, $J = 7.8$ Hz, 1H), 5.13 (s, 1H), 4.96 (s, 1H), 4.53 (s, 1H), 4.05 (dd, $J = 8.1, 2.4$ Hz, 1H), 3.98–3.85 (m, 1H), 3.71–3.64 (m, 1H), 3.48 (dd, $J = 15.2, 8.1$ Hz, 1H), 3.30–3.13 (m, 2H), 3.20 (dd, $J = 15.2, 2.4$ Hz, 1H), 1.73 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform- d) δ 167.8, 143.3, 140.4, 139.5, 131.1, 129.8, 126.1, 124.6, 123.0, 122.9, 121.5, 118.1, 112.8, 64.6, 50.7, 49.5, 27.5, 17.9; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{OClS}$, 347.0979; found, 347.0977.

7-Methyl-2-(prop-1-en-2-yl)-4-(2-(thiophen-2-yl)ethyl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2m).—Prepared from 5-methyl-*N*-(3-methylbut-2-

en-1-yl)-2-nitro-*N*-(2-(thiophen-2-yl)ethyl) benzamide (25 mg, 0.07 mmol) and purified following the procedure C; afforded 12.3 mg (54% yield) of the product as a light yellow oil: $R_f = 0.4$ (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform- d) δ 7.56 (s, 1H), 7.14 (dd, $J = 5.0, 0.7$ Hz, 1H), 7.05 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.92 (dd, $J = 5.0, 3.5$ Hz, 1H), 6.87 (d, $J = 2.9$ Hz, 1H), 6.63 (d, $J = 8.0$ Hz, 1H), 5.06 (s, 1H), 4.90 (s, 1H), 3.98 (dd, $J = 8.1, 3.1$ Hz, 1H), 3.92–3.82 (m, 1H), 3.71–3.64 (m, 1H), 3.41 (dd, $J = 15.1, 8.3$ Hz, 1H), 3.20 (dd, $J = 15.1, 3.1$ Hz, 1H), 3.27–3.11 (m, 2H), 2.27 (s, 3H), 1.69 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, Chloroform- d) δ 169.8, 144.9, 141.6, 133.1, 131.5, 129.9, 127.0, 125.5, 125.4, 123.8, 119.7, 113.3, 112.5, 65.8, 51.4, 50.4, 28.6, 20.3, 19.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{OS}$, 327.1526; found, 327.1522.

4-Benzyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]-diazepin-5-one (2n).—Prepared from *N*-benzyl-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide (43 mg, 0.133 mmol) and purified following the procedure C; afforded 34.9 mg (90% yield) of the product as a yellow viscous liquid: $R_f = 0.5$ (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.85 (dd, $J = 7.8, 1.1$ Hz, 1H), 7.35–7.23 (m, 6H), 6.89 (t, $J = 7.5$ Hz, 1H), 6.66 (d, $J = 8.0$ Hz, 1H), 5.05 (d, $J = 14.8$ Hz, 1H), 5.02 (s, 1H), 4.89 (s, 1H), 4.54 (d, $J = 14.8$ Hz, 1H), 3.95 (dd, $J = 8.4, 2.9$ Hz, 1H), 3.80 (s, 1H), 3.51 (dd, $J = 15.1, 8.4$ Hz, 1H), 3.28 (dd, $J = 15.1, 2.9$ Hz, 1H), 1.65 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, Chloroform-*d*) δ 169.9, 145.4, 144.5, 137.2, 132.3, 132.0, 128.7, 128.3, 127.5, 122.6, 119.5, 119.1, 112.9, 65.3, 51.3, 48.6, 19.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}$, 293.1648; found, 293.1646.

4-Benzyl-9-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2o).—Prepared from *N*-benzyl-3-methyl-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide (32 mg, 0.095 mmol) and purified following the procedure C; afforded 15.4 mg (53% yield) of the product as a thick yellow oily liquid: $R_f = 0.6$ (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.73 (d, $J = 7.7$ Hz, 1H), 7.35–7.28 (m, 5H), 7.20 (d, $J = 7.7$ Hz, 1H), 6.82 (t, $J = 7.6$ Hz, 1H), 5.07 (d, $J = 14.8$ Hz, 1H), 5.06 (s, 1H), 4.91 (s, 1H), 4.54 (d, $J = 14.8$ Hz, 1H), 4.09–3.90 (m, 1H), 3.52 (dd, $J = 15.0, 8.0$ Hz, 1H), 3.27 (dd, $J = 15.0, 2.8$ Hz, 1H), 2.21 (s, 3H), 1.66 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform-*d*) δ 170.2, 145.1, 142.2, 137.2, 133.4, 130.3, 128.7, 128.4, 127.5, 124.9, 123.0, 119.1, 113.3, 65.1, 51.4, 48.4, 19.1, 18.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}$, 307.1805; found, 307.1803.

5-(2,6-Dimethylbenzyl)-9-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2p).—Prepared from *N*-(2,6-dimethylbenzyl)-3-methyl-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide (42 mg, 0.115 mmol) and purified following the procedure C; afforded 31.8 mg (83% yield) of the product as a light yellow oil: $R_f = 0.44$ (4:1 PE/EA); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, $J = 7.7$ Hz, 1H), 7.39–7.31 (m, 1H), 7.19–7.12 (m, 1H), 7.06 (d, $J = 7.4$ Hz, 2H), 6.79 (t, $J = 7.6$ Hz, 1H), 5.23 (d, $J = 14.6$ Hz, 1H), 4.77 (d, $J = 13.8$ Hz, 2H), 4.70 (d, $J = 14.6$ Hz, 1H), 3.69 (dd, $J = 9.7, 2.8$ Hz, 2H), 3.39 (dd, $J = 14.9, 9.7$ Hz, 1H), 2.93 (dd, $J = 14.9, 2.8$ Hz, 1H), 2.38 (s, 6H), 2.18 (s, 3H), 1.41 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform-*d*) δ 170.0, 146.0, 142.3, 138.5, 133.4, 132.1, 130.4, 128.6, 127.9, 124.5, 122.7, 118.7, 112.6, 65.8, 47.0, 43.8, 20.2, 18.7, 18.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}$, 335.2118; found, 335.2124.

4,9-Dimethyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e]-[1,4]diazepin-5-one (2q).—Prepared from *N*-3-dimethyl-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide (60 mg, 0.229 mmol) and purified following the procedure C; afforded 34.8 mg (66% yield) of the product as a yellow solid: $R_f = 0.35$ (2:1 PE/EA), mp 132–134 °C; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.60 (dd, $J = 7.7, 0.8$ Hz, 1H), 7.16 (d, $J = 7.2$ Hz, 1H), 6.78 (t, $J = 7.6$ Hz, 1H), 5.21 (s, 1H), 4.98 (s, 1H), 4.22 (dd, $J = 6.7, 3.1$ Hz, 1H), 3.56 (dd, $J = 15.0, 6.7$ Hz, 1H), 3.42 (dd, $J = 15.0, 3.1$ Hz, 1H), 3.14 (s, 3H), 2.20 (s, 3H), 1.78 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform-*d*) δ 170.3, 144.9, 142.5, 133.2, 129.9, 124.9, 123.6, 119.2, 113.5, 65.1, 51.1, 36.3, 19.3, 18.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}$, 231.1492; found, 231.1491.

4-(4-Fluorophenethyl)-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2r).—Prepared from *N*-(4-fluorophenethyl)-*N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide (150 mg, 0.421 mmol) and purified following the procedure C; afforded 68.3 mg (50% yield) of the product as a thick yellow liquid: $R_f = 0.5$ (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.76 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.25–7.18 (m, 3H), 7.00–6.95 (m, 2H), 6.90 (t, $J = 7.4$ Hz, 1H), 6.68 (d, $J = 7.8$ Hz, 1H), 5.05 (s, 1H), 4.92 (s, 1H), 4.00 (dd, $J = 8.2, 3.2$ Hz, 1H), 3.85–3.78 (m, 1H), 3.64–3.57 (m, 1H), 3.41 (dd, $J = 15.1, 8.2$ Hz, 1H), 3.18 (dd, $J = 15.1, 3.2$ Hz, 1H), 3.00–2.87 (m, 2H), 1.70 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform-*d*) δ 169.7, 161.6 (d, $J = 242.0$ Hz), 145.2, 144.5, 134.9 (d, $J = 3.0$ Hz), 132.3, 131.7, 130.4 (d, $J = 8.0$ Hz), 123.2, 119.8, 119.2, 115.4 (d, $J = 21.0$ Hz), 113.3, 65.8, 51.3, 50.5, 33.7, 19.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{OF}$, 325.1711; found, 325.1708.

4-(4-Fluorophenethyl)-7-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2s).—Prepared from *N*-(4-fluorophenethyl)-5-methyl-*N*-(3-methylbut-en-1-yl)-2-nitrobenzamide (44 mg, 0.119 mmol) and purified following the procedure C; afforded 27.3 mg (68% yield) of the product as a light yellow oil: $R_f = 0.4$ (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.56 (s, 1H), 7.21 (dd, $J = 8.0, 5.6$ Hz, 2H), 7.06 (d, $J = 7.2$ Hz, 1H), 6.98 (t, $J = 8.6$ Hz, 2H), 6.58 (d, $J = 8.1$ Hz, 1H), 5.07 (s, 1H), 4.90 (s, 1H), 3.97 (dd, $J = 8.1, 3.2$ Hz, 1H), 3.88–3.75 (m, 1H), 3.65–3.57 (m, 1H), 3.40 (dd, $J = 15.0, 8.1$ Hz, 1H), 3.17 (dd, $J = 15.0, 3.2$ Hz, 1H), 3.01–2.88 (m, 2H), 2.28 (s, 3H), 1.70 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform-*d*) δ 169.9, 161.6 (d, $J = 243.0$ Hz), 145.4, 142.1, 134.9 (d, $J = 3.0$ Hz), 133.1, 131.5, 130.3 (d, $J = 8.0$ Hz), 129.3, 123.5, 119.4, 115.3 (d, $J = 21.0$ Hz), 113.1, 65.8, 51.2, 50.4, 33.7, 20.3, 19.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{FN}_2\text{O}$, 339.1867; found, 339.1867.

4-(4-Fluorophenethyl)-9-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2t).—Prepared from *N*-(4-fluorophenethyl)-3-methyl-*N*-(3-methylbut-2-en-1-yl)-2-nitro benzamide (140 mg, 0.378 mmol) and purified following the procedure C; afforded 76.7 mg (60% yield) of the product as a light yellow oil: $R_f = 0.4$ (2:1 PE/EA); ^1H NMR (600 MHz, Chloroform-*d*) δ 7.70–7.61 (m, 1H), 7.56–7.45 (m, 1H), 7.22–7.18 (m, 2H), 6.98 (t, $J = 8.4$ Hz, 2H), 6.80 (t, $J = 7.5$ Hz, 1H), 5.11 (s, 1H), 4.94 (s, 1H), 4.03 (dd, $J = 7.4, 2.4$ Hz, 1H), 3.88–3.84 (m, 1H), 3.59–3.54 (m, 1H), 3.43 (dd, $J = 15.0, 7.4$ Hz, 1H), 3.21 (dd, $J = 15.0, 2.4$ Hz, 1H), 2.99–2.89 (m, 2H), 2.19 (s, 3H), 1.71 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform-*d*) δ 170.1, 161.6 (d, $J = 243.0$ Hz), 145.0, 142.5, 135.0 (d, $J = 3.0$ Hz), 133.3, 130.3 (d, $J = 8.0$ Hz), 130.0, 125.0, 123.6, 119.2, 115.4 (d, $J = 21.0$ Hz), 113.5, 65.6, 51.3, 50.3, 33.7, 19.1, 18.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{OF}$, 339.1867; found, 339.1868.

4-(Furan-2-ylmethyl)-2-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2u).—Prepared from *N*-(2,3-dimethylbut-2-en-1-yl)-*N*-(furan-2-ylmethyl)-2-nitrobenzamide (47 mg, 0.143 mmol) and purified following the procedure C; afforded 33.9 mg (80% yield) of the product as a light yellow oil: $R_f = 0.43$ (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.77 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.34 (d, $J = 1.2$ Hz, 1H), 7.29–7.17 (m, 1H), 6.92 (t, $J = 7.5$ Hz, 1H), 6.67 (d, $J = 7.7$ Hz, 1H),

6.32–6.27 (m, 2H), 5.36 (s, 1H), 5.10 (d, J = 15.4 Hz, 1H), 5.00 (s, 1H), 4.30 (d, J = 15.4 Hz, 1H), 3.46 (d, J = 15.3 Hz, 1H), 3.28 (d, J = 15.3 Hz, 1H), 1.85 (s, 3H), 1.29 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, Chloroform- d) δ 169.8, 151.1, 147.1, 142.2, 132.1, 131.6, 124.5, 120.6, 120.3, 114.1, 110.4, 108.6, 67.2, 52.1, 43.8, 24.9, 19.8; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_2$, 297.1598; found, 297.1595.

4-(2,6-Dimethylbenzyl)-9-methyl-2-vinyl-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2v).—Prepared from *N*-(2,6-dimethylbenzyl)-3-methyl-

N-(3-methylbut-2-en-1-yl)-2-nitrobenzamide (70 mg, 0.199 mmol) and purified following the procedure C; afforded 47.7 mg (75% yield) of the product as a light yellow oil: R_f = 0.4 (4:1 PE/EA); ^1H NMR (400 MHz, Chloroform- d) δ 7.66 (d, J = 7.7 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.13 (d, J = 7.0 Hz, 1H), 7.06 (d, J = 7.4 Hz, 2H), 6.89 (t, J = 7.5 Hz, 1H), 5.66–5.57 (m, 1H), 5.21 (d, J = 14.6 Hz, 1H), 5.02–4.95 (m, 2H), 4.73 (d, J = 14.5 Hz, 1H), 3.74 (br, 1H), 3.24 (dd, J = 15.0, 9.8 Hz, 1H), 2.96 (dd, J = 15.0, 3.6 Hz, 1H), 2.39 (s, 6H), 2.20 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, Chloroform- d) δ 170.4, 138.9, 138.1, 133.5, 132.8, 129.9, 128.9, 128.9, 128.2, 126.3, 125.8, 120.5, 117.0, 64.6, 47.9, 44.0, 20.6, 18.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}$, 321.1961; found, 321.1969.

4-(Furan-2-ylmethyl)-2-vinyl-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2w).—Prepared from (*E*)-*N*-(but-2-en-1-yl)-*N*-(furan-2-ylmethyl)-2-nitrobenzamide (41

mg, 0.137 mmol) and purified following the procedure C; afforded 28.9 mg (79% yield) of the product as a light yellow oil: R_f = 0.42 (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform- d) δ 7.78 (dd, J = 7.7, 1.0 Hz, 1H), 7.37 (s, 1H), 7.29–7.20 (m, 2H), 6.92 (t, J = 7.5 Hz, 1H), 6.71 (d, J = 7.9 Hz, 1H), 6.34 (s, 1H), 5.80 (td, J = 17.0, 10.2 Hz, 1H), 5.27 (d, J = 17.0 Hz, 1H), 5.16 (d, J = 10.2 Hz, 1H), 5.01 (d, J = 15.3 Hz, 1H), 4.54 (d, J = 15.3 Hz, 1H), 4.06 (q, J = 5.8 Hz, 1H), 3.46 (d, J = 5.8 Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform- d) δ 169.5, 150.8, 142.9, 142.3, 136.8, 132.3, 131.8, 123.8, 120.7, 120.0, 117.3, 110.6, 108.9, 62.9, 49.5, 44.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_2$, 269.1285; found, 269.1292.

4-(4-Methoxyphenyl)-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2x).—Prepared from *N*-(4-methoxyphenyl)-*N*-(3-methylbut-2-

en-1-yl)-2-nitrobenzamide (130 mg, 0.382 mmol) and purified following the procedure C; afforded 62.4 mg (53% yield) of the product as a white solid: R_f = 0.5 (2:1 PE/EA), mp 165–167 °C; ^1H NMR (400 MHz, Chloroform- d) δ 7.82 (d, J = 7.8 Hz, 1H), 7.31–7.28 (m, 3H), 6.94–6.92 (m, 3H), 6.84 (d, J = 6.4 Hz, 1H), 5.15 (s, 1H), 4.95 (s, 1H), 4.32 (dd, J = 8.3, 3.0 Hz, 1H), 3.99 (dd, J = 14.9, 8.3 Hz, 1H), 3.82 (s, 3H), 3.76 (dd, J = 14.9, 3.0 Hz, 1H), 1.64 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform- d) δ 169.8, 158.1, 145.1, 144.7, 136.6, 132.6, 132.2, 127.8, 123.0, 119.8, 119.2, 114.5, 113.4, 65.6, 55.5, 52.4, 19.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{21}\text{O}_2\text{N}_2$, 309.1598; found, 309.1595.

2-(Prop-1-en-2-yl)-4-(*m*-tolyl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2y).—Prepared from *N*-(3-methylbut-2-en-1-yl)-2-nitro-*N*-(*m*-tolyl)benzamide

(38 mg, 0.117 mmol) and purified following the procedure C; afforded 17.5 mg (51% yield) of the product as a light yellow oil: R_f = 0.4 (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform-

d) δ 7.83 (d, J = 7.7 Hz, 1H), 7.31–7.28 (m, 2H), 7.17–7.13 (m, 2H), 7.09 (d, J = 7.5 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 7.9 Hz, 1H), 5.13 (s, 1H), 4.93 (s, 1H), 4.32 (dd, J = 8.6, 2.7 Hz, 1H), 4.02 (dd, J = 14.9, 8.6 Hz, 1H), 3.78 (dd, J = 14.9, 2.7 Hz, 1H), 2.37 (s, 3H), 1.64 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, Chloroform-*d*) δ 169.6, 145.0, 144.4, 143.4, 139.1, 132.6, 132.1, 129.0, 127.6, 127.3, 123.5, 123.0, 119.9, 119.3, 113.5, 65.5, 52.1, 21.4, 19.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}$, 293.1648; found, 293.1651.

4-Phenyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]-diazepin-5-one (22).—Prepared from *N*-(3-methylbut-2-en-1-yl)-2-nitro-*N*-phenylbenzamide (29 mg, 0.094 mmol) and purified following the procedure C; afforded 13.3 mg (51% yield) of the product as a white solid: R_f = 0.43 (2:1 PE/EA), mp 167–169 °C; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.82 (dd, J = 7.8, 1.4 Hz, 1H), 7.41 (t, J = 7.7 Hz, 2H), 7.34 (d, J = 7.2 Hz, 2H), 7.31–7.25 (m, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 5.15 (s, 1H), 4.93 (s, 1H), 4.30 (dd, J = 8.2, 3.0 Hz, 1H), 4.04 (dd, J = 14.9, 8.2 Hz, 1H), 3.93 (s, 1H), 3.82 (dd, J = 14.9, 3.0 Hz, 1H), 1.62 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform-*d*) δ 169.7, 145.0, 144.7, 143.5, 132.7, 132.2, 129.2, 126.7, 126.6, 122.9, 119.8, 119.2, 113.6, 65.5, 52.0, 19.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{19}\text{ON}_2$, 279.1492; found, 279.1490.

(E)-4-Benzyl-9-methyl-2-(6-methylhepta-2,5-dien-2-yl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (2a₁).—Prepared from (*E*)-*N*-benzyl-*N*-(3,7-dimethylocta-2,6-dien-1-yl)-3-methyl-2-nitro-benzamide (37 mg, 0.091 mmol) and purified following the procedure C; afforded 16.7 mg (49% yield) of the product as a light yellow oil: R_f = 0.6 (2:1 PE/EA); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, J = 7.1 Hz, 1H), 7.34–7.28 (m, 5H), 7.18 (d, J = 7.1 Hz, 1H), 6.80 (t, J = 7.5 Hz, 1H), 5.42 (t, J = 7.0 Hz, 1H), 5.06 (t, J = 7.1 Hz, 1H), 4.96 (d, J = 14.7 Hz, 1H), 4.60 (d, J = 14.8 Hz, 1H), 3.98 (dd, J = 8.4, 2.7 Hz, 1H), 3.55 (dd, J = 15.0, 8.4 Hz, 1H), 3.21 (dd, J = 15.0, 2.7 Hz, 1H), 2.69 (t, J = 7.0 Hz, 2H), 2.18 (s, 3H), 1.70 (s, 3H), 1.63 (s, 3H), 1.55 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, Chloroform-*d*) δ 170.3, 142.8, 137.3, 134.8, 133.3, 132.4, 130.3, 128.6, 128.3, 127.5, 126.8, 124.7, 122.7, 121.9, 118.7, 66.9, 51.3, 48.7, 26.7, 25.7, 18.3, 17.8, 13.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{31}\text{N}_2\text{O}$, 375.2431; found, 375.2438.

Preparation of Deuterated Compound 1aa'.

See page S55 in the Supporting Information. Compounds **4b–4f** were obtained according to ref 37. Preparation method of compound **1aa'** was consistent with the procedure of compound **1aa**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Bioactive molecules containing a benzodiazepine nucleus.

Figure 2.
X-ray crystal structure of compound **2z**. Ellipsoids are shown at the 50% probability level for the ORTEP diagram of the structure.

This work

Scheme 1.
Synthesis of Benzodiazepine Derivatives

Scheme 2.
Exploration of Reaction Mechanism

Scheme 3.
Postulated Mechanism

Table 1.

Screening Optimal Conditions^a

entry	variation from the standard conditions	2a yield (%) ^b	3a yield (%) ^b
1	none	90	
2	MoO ₂ Cl ₂ (dmf) ₂ instead of MoO ₂ (acac) ₂ and Cu(CF ₃ SO ₃) ₂	20	35
3	MoO ₂ (acac) ₂ without Cu(CF ₃ SO ₃) ₂	52	20
4	Mo(CO) ₆ instead of MoO ₂ (acac) ₂ and Cu(CF ₃ SO ₃) ₂	40	trace
5	CoMoO ₄ instead of MoO ₂ (acac) ₂ and Cu(CF ₃ SO ₃) ₂	11	trace
6	Pt(acac) ₂ instead of MoO ₂ (acac) ₂ and Cu(CF ₃ SO ₃) ₂	trace	
7	Ni(PPh ₃) ₂ Cl ₂ instead of MoO ₂ (acac) ₂ and Cu(CF ₃ SO ₃) ₂	N.R. ^c	
8	Fe(OAc) ₂ instead of MoO ₂ (acac) ₂ and Cu(CF ₃ SO ₃) ₂	N.R.	
9	Pd(OAc) ₂ instead of MoO ₂ (acac) ₂ and Cu(CF ₃ SO ₃) ₂	N.R.	
10	CuCl ₂ instead of MoO ₂ (acac) ₂ and Cu(CF ₃ SO ₃) ₂	N.R.	
11	Cu(CF ₃ SO ₃) ₂ without MoO ₂ (acac) ₂	N.R.	
12	Ru ₃ (CO) ₁₂ instead of MoO ₂ (acac) ₂ and Cu(CF ₃ SO ₃) ₂	N.R.	
13	Rh(CO) ₂ (C ₅ H ₇ O ₂) instead of MoO ₂ (acac) ₂ and Cu(CF ₃ SO ₃) ₂	N.R.	
14	W(CO) ₆ instead of MoO ₂ (acac) ₂ and Cu(CF ₃ SO ₃) ₂	N.R.	
15	Cr(acac) ₃ instead of MoO ₂ (acac) ₂ and Cu(CF ₃ SO ₃) ₂	N.R.	
16	MoO ₂ Cl ₂ (dmf) ₂ CuCl ₂ instead of MoO ₂ (acac) ₂ and Cu(CF ₃ SO ₃) ₂	45	
17	MoO ₂ Cl ₂ (dmf) ₂ instead of MoO ₂ (acac) ₂	66	10
18	CH ₂ Cl ₂ instead of toluene	N.R.	
19	THF instead of toluene	N.R.	
20	CH ₃ CN instead of toluene	N.R.	
21	DMF instead of toluene	N.R.

entry	variation from the standard conditions	2a yield (%) ^b	3a yield (%) ^b
22	DMSO instead of toluene	N.R.	
23	(CH ₃) ₃ P instead of PPh ₃	N.R.	
24	S-(−)-BINAP instead of PPh ₃	43	
25	Xantphos instead of PPh ₃	51	
26	no PPh ₃	N.R.	
27	30 °C instead of 110 °C	N.R.	
28	60 °C instead of 110 °C	N.R.	
29	80 °C instead of 110 °C	5	
30	140 °C (xylene) instead of 110 °C	87	
31	4 h instead of 12 h	53	
32	8 h instead of 12 h	80	
33	16 h instead of 12 h	90	

^aReaction conditions: **1aa** (0.16 mmol), MoO₂(acac)₂ (10 mol %), Cu(CF₃SO₃)₂ (10 mol %), PPh₃ (2.5 equiv), and toluene (2 mL) under N₂ at 110 °C for 12 h.

^bIsolated yield.

^cNo reaction

Table 2.

Formation of Diazepine Derivatives from the Aromatic Nitro Derivatives^a

^aReaction conditions: substrate (1 equiv)/MoO₂(acac)₂ (10%)/Cu(CF₃SO₃)₂(10%)/PPh₃(2.5 equiv)/toluene under N₂ at 110 °C for 12 h.