Parallel Synthesis of 1,3-Dihydro-1,4-benzodiazepine-2-ones Employing Catch and Release

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An efficient solid-phase method has been developed for the parallel synthesis of 1,3-dihydro-1,4-benzodiazepine-2-one derivatives. A key step in this procedure involves catching crude 2-aminobenzoimine products **4** on an amino acid Wang resin **10**. Mild acidic conditions then promote a ring closure and in the same step cleavage from the resin to give pure benzodiazepine products **12**. The 2-aminobenzoimines **4** can be synthesized from either 2-aminobenzonitriles **1** and Grignard reagents **2** or from iodoanilines **5** and nitriles **7** allowing a range of diversification. Further diversification can be introduced to the benzodiazepine products by N-alkylation promoted by a resin bound base and alkylating agents **13**.

Introduction

Benzodiazepines **12** are categorized as privileged structures[1] because of their ability to interact with a wide range of different enzymes and receptors. For many years they have been of great interest in medicinal chemistry because of their widespread biological activities including anxiolytic, anticonvulsant, and hypnotic activities,[2] resulting from their interaction with $GABA_A$ receptors. In addition derivatives have been identified that are highly selective cholecystokinin receptor A and receptor B antagonists,[3] reverse transcriptase inhibitors,[4] ras farnesyl transferase inhibitors,[5] oxytocin antagonists,[6] opioid receptor ligands,[7] platelet-activating factor antagonists,[8] and human immunodeficiency virus transactivator Tat antagonists.[9] Due to the many different activities, benzodiazepines have been targets of a number of solution- and solid-phase synthetic studies. [3,10–12] In 1992, Ellman[10] was the first to publish a solid-phase protocol employing in seven steps three components, i.e., 2-aminobenzophenones, amino acids, and alkylating agents. The 2-aminobenzophenone derivatives were attached to the solid support through either hydroxy or carboxylic acid functionality. The amine functionality was then coupled with a Fmoc protected amino acid fluoride to give an amide bond. Upon removal of the Fmoc group and treatment with acetic acid, imine formation was promoted to give the benzodiazepine ring system **12**. N-alkylation of the amide and cleavage from the resin yielded the final benzodiazepine products. The year after (1993) DeWitt et al[11] described another synthetic approach, which in a number of ways had improvements compared to Ellmans protocol. Here an amino acid on solid support was reacted with a 2-aminobenzoimine making a new imine bond. Acid-promoted amide formation then led to ring closure and at the same time cleavage from the resin. In this way, there was no need to use activated amino acids. No trace from the solid phase was left on the products and the benzodiazepines were made in only three steps. More interesting synthetic work has been published on solid-phase preparation of benzodiazepinones,[12] but this is not considered further in this manuscript.

The work described in this article takes its starting point in DeWitts protocol. Instead of using pure 2-aminobenzoimines, two methods were developed for the synthesis of these (Schemes 1 and 2). By catching the crude 2-aminobenzoimine products **4** on an amino acid resin **10**, the 2-aminobenzoimines were purified by amino acid imine formation. In this way, the protocol takes advantage of the catch and release principle by using it as means for synthetic intermediate purification.

Results and Discussion

Using a protocol by Wiklund and Bergman[13] the first method for the synthesis of 2-aminobenzoimines **4** was derived by reacting 2-amino-benzonitriles **1** with two equivalents of Grignard reagent **2** (Scheme 1).

Quench of the dianions **3** with a saturated solution of NH_4Cl, separation of the phases, and evaporation of the organic phase afforded the crude 2-aminobenzoimines **4**, which were used in the next synthetic step without purification. To increase the scope of 2-aminobenzoimines **4** a second synthetic method was employed (Scheme 2). The halogen–metal exchange of iodoanilines **5** was described by Knochel et al.[14] One equivalent of PhMgCl deprotonated the amine and one equivalent of *i*PrMgCl or *i*PrMgCl·LiCl[15] acted as the metalating agent. This required R3 to be an electron withdrawing group. As the metalated compound **6** was supposed to react with a nitrile, it was not possible to have this functionality or any other reactive group as R3, but fluoro or trifluoromethyl functionality were well tolerated. Using the stronger metalating agent nBu$_3$MgLi, described earlier by Inoue et al,[16] an electron withdrawing group was no longer necessary, hence enlarging the scope of the reaction. It should be noted that electron withdrawing groups are unfavorable in the 2-aminobenzoimine products **4** as they cause decreased stability toward imine hydrolysis.

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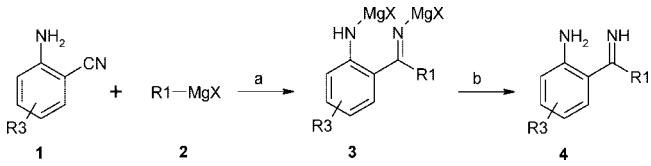
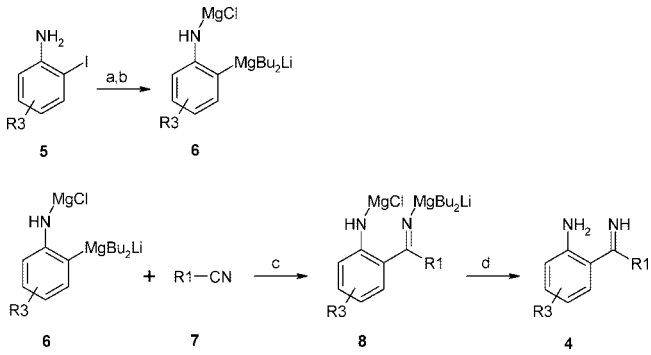
Scheme 1[a]



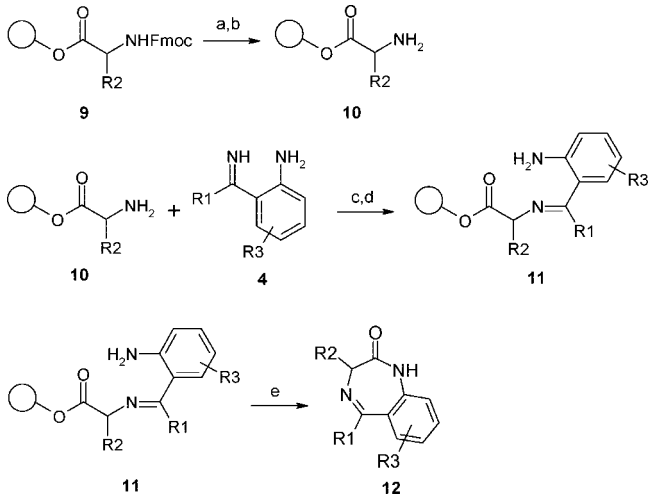
[a] Reagents and conditions: (a) THF, reflux, 3 h; (b) NH_4Cl sat. soln.

Scheme 2[a]



[a] Reagents and conditions: (a) PhMgCl, THF, −30 °C, 5 min; (b) *n*-Bu_3MgLi, 0 °C, 30 min; (c) Room temp., 30 min; (d) NH_4Cl sat. soln.

Scheme 3[a]



[a] Reagents and conditions: (a) 20% piperidine/80% DMF, room temp., 30 min; (b) Wash 5 times with DMF; (c) NMP, 140 °C, overnight; (d) Wash 4 times with NMP and 8 times with DCM; (e) 10% TFA/90% DCE, room temp., 2 h or 50% AcOH/50% DCE, room temp., 16 h.

Both methods (Schemes 1 and 2) may be performed in Radleys 24-place Greenhouse or Radleys 12-place carousel. Grignard and lithium reagents were titrated according to known procedures,[17] as it was necessary to know the exact concentrations.

After deprotection of Fmoc protected amino acid Wang resins **9**, the crude 2-aminobenzoimine **4** products were caught on the resins by the formation of a new imine bond (Scheme 3).

Reaction conditions were optimized by varying temperature, solvent, reaction time, and catalysts (Table 1).

Using conventional heating, 140 °C overnight in NMP without catalyst was found to give the best results for imine formation so these conditions were chosen for parallel synthesis. Microwave heating proved even more effective, but due to resin handling issues this was considered less practical for library preparation. For single-compound synthesis, microwave heating is preferred (*vide infra*). Impurities were removed by washing the resins **11** 4 times with NMP and 8 times with DCM, shaking for approximately 10 min between each washing. To cyclize and thereby cleave the benzodiazepines from the solid support, different reaction conditions were tested (Table 2).

Table 1. Reaction Conditions Tested in Optimization of Catch of Imine on Amino Acid Resin

solvents	pyridine, NMP, *m*-xylene, dichloroethane
temperatures	60 °C, 110 °C, 120 °C, 140 °C
reaction times	30 min (microwave), overnight (conventional heating)
catalysts	AcOH, $Sc(OTf)_3$, $Yb(OTf)_3$, $Ti(i\text{-}PrO)_4$

Table 2. Reaction Conditions Tested in Optimization of Cleavage of the Benzodiazepine Products from the Solid Support

cleavage mixtures[a]	5% TFA, 10% TFA, 25% TFA, 50% TFA, 50% AcOH
reaction times	2 h, 16 h

[a] In DCE.

Table 3. Reaction Conditions Tested in Optimization of Cleavage Mixtures of Different Concentration and Acidity

cleavage mixture	Fmoc-protected phenylalanine in solution[a]
1% TFA/99% DCE	yes
10% TFA/90% DCE	yes
50% TFA/50% DCE	yes
50% AcOH/50% DCE	no

[a] Detected by LC–MS.

It was found that all cleavage mixtures cleaved the benzodiazepine products from the solid support. In most cases unreacted amino acid was also cleaved from the solid support and found as a byproduct. It was therefore uncertain if ring closure happened concurrently with cleavage or by a two-step acid-promoted cleavage of the ester bound to the resin followed by cyclization. To investigate this further, pure Fmoc-protected phenylalanine Wang resins were treated with cleavage mixtures of different concentration and acidity. It was found that 50% AcOH was not acidic enough to cleave the bond between the amino acid and the resin (Table 3). In this way it was realized that cleavage of the benzodiazepine intermediates **11** with 50% AcOH happened only because of the intramolecular ring closure providing only the desired products **12** leaving unreacted amino acid on the resin. For this reason, catch on the resins did not have to be quantitative, which is normally a prerequisite to obtain pure products from solid-phase synthesis.

Treating the resins with a mixture of 50% AcOH and 50% DCE for 16 h at room temperature was found to be the optimal protocol (Scheme 3). The long reaction time was needed because cleavage is slow under these mild acidic conditions.

All reactions on solid phase were carried out in Bohdan MiniBlocks keeping the resins in the same reactor through the whole reaction sequence.

The efficiency of the catch and release principle can be seen from the UV trace on LC–MS of the solution after each synthetic step (Figure 1).

Table 4 shows 27 different benzodiazepines made with catch and release. Because of the mild acidic conditions used

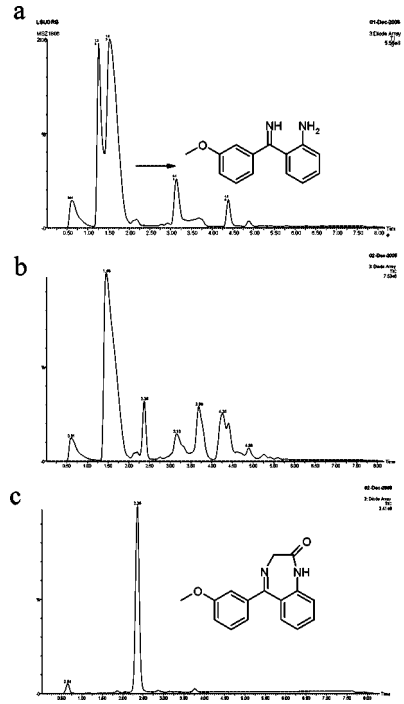


Figure 1. LC–MS spectra of solutions: (a) after 2-aminobenzophenone imine **4**formation; (b) after catch on the resin **11**; (c) after cleavage from the resin **12**.

in cleavage from the solid phase, it was possible to fully preserve protection groups on amino acid side chains in the final products.

It was found that the protocol was also useful and effective in the synthesis of benzodiazepines on a larger scale. Whereas the library syntheses (Table 4) were carried out on 0.1 mmol scale, two benzodiazepines were synthesized on 1 mmol scale using the microwave conditions mentioned earlier (see Table 1) in the imine **11** formation step (Table 5).

To introduce additional diversification in the benzodiazepine products, a method for *N*-alkylation of the anilide was developed (Scheme 4). BEMP[18] resin was chosen as the base as it was easy to filter off after the reaction. By employing the conditions in Scheme 4 two benzodiazepine derivatives **12** were alkylated with several different alkylating agents **13** in high yields (Table 6) with no over-alkylation observed. In all cases except **14(8)** HPLC purification was needed after alkylation.

Summary

A three-step protocol for the parallel synthesis of 1,3-dihydro-1,4-benzodiazepine-2-ones with diverse chemical functionality (Table 4 and 5) was developed. By employing the catch and release principle crude 2-aminobenzoimines **4** were converted to benzodiazepine products **12**, which were released from the resin in high purities. Alkylation of the benzodiazepine products introduces additional diversification (Table 6). The protocol allows the substituents around the benzodiazepine scaffold R1, R2, R3, and R4 to be varied independently and synthesis of the 2-aminobenzoimines **4** by two different methods adds to the possibility of variation.

Experimental Section

Materials and General Methods. All reagents and starting materials were purchased from commercial sources and used without further purification. Solvents were HPLC grade and dried with activated molecular sieves. Synthesis of 2-aminobenzoimine intermediates **4** was carried out using Radleys 12-place carousel reaction station and 24-place greenhouse parallel synthesizer. Library synthesis of benzodiazepines **12** was carried out using Bohdan MiniBlocks (New Brunswick Scientific) and for large-scale synthesis a microwave oven (Biotage) was used. Evaporation of compounds was carried out using a Genevac EZ-2 plus centrifuge evaporator. Analytical reverse-phase HPLC was performed using an Xterra C18 column (5 μm, 3 $\times$ 50 mm) on a Waters Alliance 2795 HPLC. Preparative reverse-phase HPLC was performed using a Luna C18(2) column (5 μm, 10 $\times$ 250 mm) on a Gilson HPLC. Mass spectra were obtained using a Waters ZQ2000 mass spectrometer with an electrospray probe and single quadrupole detector. HRMS were performed on a Micromass LCT spectrometer using an electrospray interface. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75, 125, or 150 MHz) spectra were recorded on a Bruker (300, 500, or 600 MHz) spectrometer with TMS as an internal reference. Yields determined by NMR were obtained using d_5-DMSO as internal standard. Generally, we prefer this method when handling small amounts of material since it measures the concentration of the compound of interest, not including the mass of impurities such as moisture residing on vials, salts, or residual solvents.

Representative Procedure for the Preparation of 2-Aminobenzoimine Dianions 3 from Grignard Reagents 2 and Amino Nitriles 1. Under argon atmosphere: A stirred solution of Grignard reagent **2** (1.5 mmol, 1–3 M solution in THF or Et_2O) was cooled to -50 °C. A solution of amino nitrile 1 (0.6 mmol) in THF (2 mL) was added. The reactions were then heated to reflux (70 °C) for 3 h.

Quench of dianions **3** synthesized in a Radley 12-place carousel. Approx. 5 mL of sat. NH_4Cl was added and the phases were separated. The aqueous phase was extracted with 2 $\times$ 5 mL of Et_2O. The combined organic phases were washed with 2 $\times$ 2 mL of water, 2 mL of brine, and dried with Na_2SO_4. Evaporation of the solvent gave the 2-aminobenzoimines **4** as an oil or solid which were used in the next step without further purification.

Quench of Dianions 3 Synthesized in a Radley Greenhouse. Approx. 1 mL of sat. NH_4Cl was added. The aqueous phase was removed by filtering the mixture through 0.5 g of hydromatrix in the Bohdan MiniBlock. The hydromatrix was then washed with 2 $\times$ 2 mL of Et_2O. The combined organic phases were evaporated and the 2-aminobenzoimines **4** were used without further purification.

Preparation of Lithium Tributyl Magnesate (^{n}Bu$_3$MgLi). To a stirred solution of butylmagnesium bromide (0.72 mmol, 1.2 M solution in THF) was added *n*-butyllithium (1.4 mmol, 1.4 M solution in THF) at 0 °C and the mixture was stirred

Table 4. Benzodiazepines Made with Catch and Release

compound	R1	R2	R3	yield (%)[a]	method[b]
12(1)	Et	Bn	5-Cl	4	1
12(2)	Ph	*i*-Pr	5-Cl	13	1
12(3)	Ph	Bn	5-Cl	22	1
12(4)	Ph	*i*-Bu	5-Cl	11	1
12(5)	2-thiophene	4-aminobutyl	5-Cl	7	1
12(6)	2-thiophene	H	5-Cl	7	1
12(7)	2-thiophene	*i*-Pr	5-Cl	24	1
12(8)	2-thiophene	Me	5-Cl	13	1
12(9)	2-thiophene	Bn	5-Cl	14	1
12(10)	2-thiophene	*i*-Bu	5-Cl	16	1
12(11)	3-OMePh	H	H	38	2
12(12)	3-OMePh	Me	H	19	2
12(13)	3-OMePh	*i*-Pr	H	37	2
12(14)	3-OMePh	*i*-Bu	H	17	2
12(15)	3-OMePh	*t*-BuO(O)CCH_2–	H	8	2
12(16)	3-OMePh	*t*-BuO(O)C CH_2CH_2–	H	11	2
12(17)	3-OMePh	*t*-$BuOCH_2$–	H	32	2
12(18)	Ph	H	5-Cl	53	2
12(19)	Ph	Me	5-Cl	25	2
12(20)	Ph	*t*-BuO(O)CCH_2–	5-Cl	16	2
12(21)	Ph	*t*-BuO(O)C CH_2CH_2–	5-Cl	16	2
12(22)	Ph	*t*-$BuOCH_2$–	5-Cl	34	2
12(23)	2-thiophene	Bn	H	11	2
12(24)	3-OMePh	Bn	5-Cl	11	2
12(25)	naphthyl	H	H	17	3
12(26)	naphthyl	H	4-CF_3	23	3
12(27)	3,4-dimethyl-phenyl	H	3-F, 5-Cl	38	3

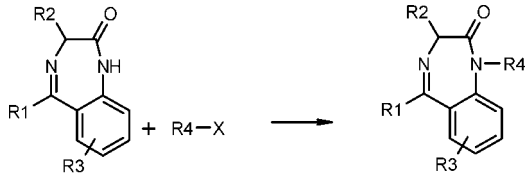
[a] Overall yield from stated loading of the Wang resin **9**. Yields are based on NMR of crude products. All products are >80% pure by NMR, and UV purities are 100%. [b] Method 1: Imine synthesis, Scheme 1. Clevage: 10% TFA/90% DCE, room temp., 2 h. Method 2: Imine synthesis, Scheme 1. Cleavage: 50% AcOH/50% DCE, room temp., 16 h. Method 3: Imine synthesis, Scheme 2. Cleavage: 50% AcOH/50% DCE, room temp., 16 h.

Table 5. Benzodiazepines Synthesized Using Microwave Conditions

compound	R1	R2	R3	yield (%)[a]	method[b]
12(18)	Ph	H	5-Cl	65	4
12(28)	Ph	4-NH(Boc)butyl	5-Cl	56	4

[a] Overall yield from stated loading of the Wang resin **9**. Yields are based on NMR of crude products. Products are 100% pure by NMR and UV. [b] Method 4: Imine synthesis, Scheme 1. Catch on resin: 120 °C, microwave, 30 min. in NMP. Cleavage: 50% AcOH/50% DCE, room temp., 16 h.

Scheme 4[a]



12 13 14

[a] Reagents and conditions: BEMP[18] resin, DMF, room temp., 4 h.

for 10 min. The formed tributyl magnesate was used directly from this cooled mixture.

Representative Procedure for the Preparation of 2-Aminobenzoimines 4 from Iodoanilines 6 and Nitriles 7. Under argon atmosphere: To a solution of iodoaniline **6** (0.6 mmol) in THF (0.5 mL) was added phenylmagnesium bromide (0.6 mmol, 1.6 M solution in THF) at −30 °C and the mixture was stirred for 10 min. Tributyl magnesate mixture (0.72 mmol) was added and the reaction was allowed to warm up to 0 °C. After 30 min the nitrile **7** was added and the reaction was stirred for a further 30 min after which the dianion **8** was formed. Approx. 1 mL of sat NH_4Cl was added, and the mixture was then shaken until two distinct phases arose. The THF phase was decanted via syringe and transferred to a microtiter plate from which the solvent was evaporated. The 2-aminobenzoimines **4** were used without further purification.

Table 6. Benzodiazepine Derivatives Alkylated with Different Alkylating Agents

Compound	Alkylating Agent	Benzodiazepine Derivative	Yield (%)[a]
14(1)		**12(18)**	52
14(2)		**12(28)**	18
14(3)		**12(18)**	52
14(4)		**12(18)**	60
14(5)		**12(18)**	20
14(6)		**12(18)**	49
14(7)		**12(18)**	41
14(8)		**12(18)**	71
14(9)		**12(18)**	38
14(10)		**12(18)**	36

[a] Isolated yield of the alkylation reaction. Products are quantified by NMR.

Representative Procedure for Catch of 2-Aminobenzoimines 4 on Amino Acid Resins 10 in Library Format. Fmoc-protected Wang amino acid resins **9** (0.1 mmol, 100–200 mg) were weighed out into the Bohdan MiniBlock. To deprotect the resins, they were treated with 1.6 mL of DMF and 0.4 mL of piperidine for 30 min and then washed with 5 × 2 mL of DMF. The 2-aminobenzoimines **4** were

dissolved in 2 mL of NMP and transferred to the resins in the MiniBlock. The reactions were shaken overnight at 140 °C on the Bohdan Shaker. After filtration the resins **11** were washed with 4 × 2 mL of NMP and 8 × 2 mL of DCM, standing on the Shaker for 5–10 min between each washing.

Cleavage from the Resins 11 Giving 1,3-Dihydro-1,4-benzodiazepine-2-ones 12 in Library Format. Method 1 (12(1)–12(10)). Cleavage mixture (2 mL, 10% TFA/90% DCE) was transferred to the resins in the MiniBlock which was then left on the shaker for 2 h. The cleavage mixture was filtered off into a microtiter plate and the resins were washed with 2 × 2 mL of DCM. The reaction filtrate and washings were evaporated and the residues were dissolved in 2 mL of DCM. To remove unreacted amino acid and traces of TFA the DCM phase was washed with 1 mL of sat $NaHCO_3$. The aqueous phase was removed by filtering through 0.5 g of hydromatrix in the MiniBlock. Washing the hydromatrix with DCM and evaporation of the combined phases gave the desired 1,3-dihydro-1,4-benzodiazepine-2-ones. Yields: 4–24%.

3-Benzyl-7-chloro-5-ethyl-1,3-dihydro-benzo[e][1,4]-diazepin-2-one 12(1). ^{1}H NMR ($(CD_3)_2SO$) δ: 7.75 (d, 1H, J = 2.4 Hz), 7.52 (dd, 1H, J = 8.7, 2.4 Hz), 7.10–7.27 (m, 6H), 3.53 (t, 1H, J = 6.78 Hz, –C *H*–CH_2–Ar), 3.32 (dd, 1H, J = 12.00, 7.56 Hz, –CH_2–Ar), 3.18 (dd, 1H, J = 13.68, 8.07 Hz, –CH_2–Ar), 2.80 (m, 1H, –*CH_2*–CH_3), 2.64 (m, 1H, – *CH_2*–CH_3), 0.98 (t, 3H, J =7.29Hz, –CH_2– *CH_3*). ^{13}C NMR ($(CD_3)_2SO$) δ: 169.77, 169.54, 139.10, 136.38, 130.82, 129.51 (2C), 129.19, 127.84 (2C), 127.40, 127.15, 125.79, 122.77, 63.92, 36.90, 30.56, 10.90. HRMS (ES) *m*/*z* calcd for (M^+) $C_{18}H_{17}ClN_2O$, 313.1107; found, 313.1113.

7-Chloro-3-isopropyl-5-phenyl-1,3-dihydro-benzo[e][1,4]-diazepin-2-one 12(2). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.64 (s, 1H, –NH), 7.64 (dd, 1H, J = 8.73, 2.52 Hz), 7.43–7.54 (m, 5H), 7.28 (d, 1H, J = 8.76 Hz), 7.25 (d, 1H, J = 2.43 Hz), 3.07 (d, 1H, J = 8.82 Hz, –C *H*–CH–$(CH_3)_2$), 2.51 (m, 1H, –CH–C *H*–$(CH_3)_2$), 1.12 (d, 3H, J = 6.69 Hz, –CH_3), 0.98 (d, 3H, J = 6.54 Hz, –CH_3). ^{13}C NMR ($(CD_3)_2SO$) δ: 169.23, 166.14, 138.46, 138.12, 131.41, 130.30, 129.32, 129.15 (2C), 128.30 (2C), 127.73, 126.36, 123.00, 68.88, 28.54, 19.83, 18.61. HRMS (ES) *m*/*z* calcd for (M^+) $C_{18}H_{17}ClN_2O$, 313.1107; found, 313.1092.

3-Benzyl-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]-diazepin-2-one 12(3). ^{1}H NMR ($(CD_3)_2SO$) δ: 8.84 (bs, 1H, –NH), 7.61 (dd, 1H, J= 8.79, 2.28 Hz, arom H), 7.16–7.50 (m, 12 H, arom H), 3.72 (dd, 1H, J = 8.04, 6.12 Hz, –C *H*–CH_2–Ar), 3.28–3.46 (m, 2H, –CH– *CH_2*–Ar). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.33, 166.92, 139.49, 138.76, 138.58, 131.97, 130.81, 130.05 (2C), 129.80, 129.60 (2C), 128.72 (2C), 128.40 (2C), 128.16, 126.88, 126.36, 123.57, 65.24, 37.45. HRMS (ES) *m*/*z* calcd for (M^+) $C_{22}H_{17}ClN_2O$, 361.1107; found, 361.1097.

7-Chloro-3-isobutyl-5-phenyl-1,3-dihydro-benzo[e][1,4]-diazepin-2-one 12(4). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.30 (bs, 1H, –NH), 7.64 (dd, 1H, J = 8.70, 2.46 Hz), 7.45–7.55 (m, 5H), 7.28 (d, 1H, J = 8.73 Hz), 7.25 (d, 1H, J = 2.40 Hz), 3.51 (dd, 1H, J = 9.00, 4.74 Hz, =N–C *H*–(C=O)–CH_2–), 2.03–2.07 (m, 1H, –C *H*–$(CH_3)_2$), 1.80–1.93 (m, 2H, –CH–*CH_2*–CH–), 0.96 (d, 3H, J = 6.42 Hz, –CH– *CH_3*), 0.80 (d, 3H, J = 6.36 Hz, –CH– *CH_3*). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.30, 166.45, 138.44, 138.18, 131.47, 130.28, 129.33, 129.14 (2C), 128.27 (2C), 127.75, 126.34, 123.00, 79.08, 61.29, 24.12, 23.32, 21.74. HRMS (ES) *m*/*z* calcd for (M^+) $C_{19}H_{19}ClN_2O$, 327.1264; found, 327.1265.

3-(4-Amino-butyl)-7-chloro-5-thiophen-2-yl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(5). ^{1}H NMR ($(CD_3)_2SO$) δ: 7.73 (dd, 1H, J = 3.81, 1.89 Hz), 7.64–7.68 (m, 2H), 7.26 (d, 1H, J = 9.18 Hz), 7.13 (d, 1H, J = 2.31 Hz), 7.12 (s, 1H), 3.31 (t, 1H, J = 6.87 Hz, –C *H*–CH_2–), 1.87–1.99 (m, 2H, –CH_2–), 1.30–1.40 (m, 6H, aliphatic H). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.60, 160.26, 143.26, 137.69, 131.63, 130.90, 130.59, 128.94, 127.89, 127.08, 126.76, 123.08, 62.61, 40.90, 30.38, 29.69, 22.67. HRMS (ES) *m*/*z* calcd for (M^+) $C_{17}H_{18}ClN_3OS$, 348.0937; found, 348.0955.

7-Chloro-5-thiophen-2-yl-1,3-dihydro-benzo[e][1,4]-diazepin-2-one 12(6). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.52 (bs, 1H, –NH), 7.75 (t, 1H, J = 3.03 Hz), 7.66 (dd, 1H, J = 8.4, 2.28 Hz), 7.64 (d, 1H, J = 2.67 Hz), 7.26 (d, 1H, J = 8.4 Hz), 7.13 (d, 1H, J = 3.45 Hz), 7.13 (s, 1H), 2.29 (bs, 2H, –CH_2–). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.81, 162.50, 143.81, 138.50, 132.09, 131.54, 131.19, 129.64, 128.34, 127.24, 127.22, 123.57, 56.77. HRMS (ES) *m*/*z* calcd for (M^+) $C_{13}H_9ClN_2OS$, 277.0202; found, 277.0222.

7-Chloro-3-isopropyl-5-thiophen-2-yl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(7). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.61 (bs, 1H, –NH), 7.73 (t, 1H, J = 3.03 Hz), 7.64–7.68 (m, 2H), 7.26 (dd, 1H, J = 7.62, 1.14 Hz), 7.12–7.14 (m, 2H), 3.07 (d, 1H, J = 8.79 Hz, –C *H*–CH–$(CH_3)_2$), 2.40–2.47 (m, 1H, –CH–C *H*–$(CH_3)_2$), 1.05 (d, 3H, J = 6.87 Hz, –CH_3), 0.95 (d, 3H, J = 6.87 Hz, –CH_3). ^{13}C NMR ($(CD_3)_2SO$) δ: 169.50, 159.91, 143.33, 137.61, 131.57, 130.70, 130.50, 128.88, 127.85, 126.89, 126.76, 123.03, 68.30, 28.25, 19.69, 18.46. HRMS (ES) *m*/*z* calcd for (M^+) $C_{16}H_{15}ClN_2OS$, 319.0672; found, 319.0661.

7-Chloro-3-methyl-5-thiophen-2-yl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(8). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.60 (s, 1H, –NH), 7.74 (dd, 1H, J = 4.20, 1.53 Hz), 7.66 (dd, 1H, J = 7.26, 2.67 Hz), 7.65 (d, 1H, J = 2.28 Hz), 7.25 (d, 1H, J = 9.57 Hz), 7.12 (d, 1H, J = 3.06 Hz), 7.11 (s, 1H), 3.69 (q, 1H, J = 6.12 Hz, –C *H*–CH_3), 1.46 (d, 3H, J = 6.12 Hz, –CH– *CH_3*). ^{13}C NMR ($(CD_3)_2SO$) δ: 171.34, 160.08, 143.20, 137.68, 131.60, 131.02, 130.60, 128.92, 127.86, 127.19, 126.70, 123.03, 58.02, 16.85. HRMS (ES) *m*/*z* calcd for (M^+) $C_{14}H_{11}ClN_2OS$, 291.0359; found, 291.0360.

3-Benzyl-7-chloro-5-thiophen-2-yl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(9). ^{1}H NMR ($(CD_3)_2SO$) δ: 9.55 (bs, 1H, –NH), 7.73 (dd, 1H, J = 4.2, 1.92 Hz), 7.64 (dd, 1H, J = 8.43, 2.31 Hz), 7.60 (d, 1H, J = 2.28 Hz), 7.14–7.35 (m, 6H), 7.11 (d, 1H, J = 2.31 Hz), 7.10 (s, 1H), 3.72 (dd, 1H, J = 8.01, 5.34 Hz, –C *H*–CH_2–Ar), 3.27–3.37 (m, 2H, –CH– *CH_2*–Ar). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.60, 160.66, 143.61, 139.35, 138.06, 132.14, 131.39, 131.23, 130.04 (2C), 129.39, 128.31 (3C), 127.37, 127.30, 126.32, 123.60, 64.75, 37.20. HRMS (ES) *m*/*z* calcd for (M^+) $C_{20}H_{15}ClN_2OS$, 367.0672; found, 367.0670.

7-Chloro-3-isobutyl-5-thiophen-2-yl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(10). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.30 (bs, 1H, –NH), 7.73 (dd, 1H, J = 3.00, 1.53 Hz),

7.65–7.68 (m, 2H), 7.27 (d, 1H, $J = 9.18$ Hz), 7.13 (d, 1H, $J = 2.7$ Hz), 7.11 (s, 1H), 3.52 (dd, 1H, $J = 8.79$, 4.95 Hz, =N–C *H*–(C=O)–), 1.91–2.00 (m, 1H, –CH–$(CH_3)_2$), 1.77–1.81 (m, 2H, –CH_2–), 0.92 (d, 3H, $J = 6.09$ Hz, –CH_3), 0.78 (d, 1H, $J = 6.12$ Hz, –CH_3). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.58, 160.24, 143.32, 137.74, 131.68, 130.83, 130.60, 128.94, 127.89, 126.99, 126.78, 123.11, 79.10, 60.90, 24.15, 23.16, 21.88. HRMS (ES) *m*/*z* calcd for (M^+) $C_{17}H_{17}ClN_2OS$, 333.0828; found, 333.0824.

Cleavage from the Resins 11 Giving 1,4-Benzodiazepine-2-ones 12 in Library Format. Method 2 and 3 (12(11)–12(27)). Cleavage mixture (2 mL, 50% AcOH/50% DCE) was transferred to each of the resins in the MiniBlock which was then left on the shaker for 16 h. The solution was filtered off into a microtiter plate and the resins were washed with 2 × 2 mL of DCM. The reaction filtrate and washings were evaporated. To remove traces of AcOH the residues were dissolved in 1 mL of DCM + 1 mL of hexane and evaporated which gave the desired 1,4-benzodiazepine-2-ones **12**. Yields: 11–53%.

5-(3-Methoxy-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(11). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.53 (bs, 1H, –NH), 7.56 (td, 1H, $J = 5.61$, 1.59 Hz, arom H), 7.33 (td, 1H, $J = 6.54$, 0.93 Hz, arom H), 7.24–7.27 (m, 2H, arom H), 7.17 (td, 1H, $J = 7.2$, 0.81 Hz, arom H), 7.08 (d, 1H, $J = 1.05$ Hz, arom H), 7.07 (dd, 1H, $J = 6.87$, 0.81 Hz, arom H), 6.94 (d, 1 H, $J = 7.14$Hz, arom H), 4.12 (bs, 2 H, –CH_2–), 3.77 (s, 3H, –OCH_3). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.29, 169.30, 158.95, 140.41, 139.47, 131.46, 130.58, 129.17, 126.13, 122.5, 121.84, 120.99, 115.90, 114.05, 56.87, 55.07. HRMS (ES) *m*/*z* calcd for (M^+) $C_{16}H_{14}N_2O_2$, 267.1133; found, 267.1114.

5-(3-Methoxy-phenyl)-3-methyl-1,3-dihydro-benzo[e][1,4]-diazepin-2-one 12(12). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.52 (bs, 1H, –NH), 7.59 (t, 1H, $J = 6.87$ Hz, arom H), 7.33 (t, 1H, $J = 7.86$ Hz, arom H), 7.26 (td, 2H, $J = 7.89$, 1.56 Hz, arom H), 7.17 (td, 1H, $J = 7.38$, 0,57 Hz, arom H), 7.02–7.07 (m, 2H, arom H), 6.96, (dd, 1H, $J = 7.77$, 0,78 Hz, arom H), 3.76 (s, 3H, –OCH_3), 3.62 (q, 1H, $J = 6.39$ Hz, –CH–), 1.53 (d, 3H, $J = 6.36$ Hz, –CH_3). ^{13}C NMR ($(CD_3)_2SO$) δ: 171.22, 167.16, 158.91, 140.20, 139.06, 131.42, 130.24, 129.18, 126.48, 122.45, 121.81, 120.94, 115.56, 114.40, 58.38, 55.07, 17.12. HRMS (ES) *m*/*z* calcd for (M^+) $C_{17}H_{16}N_2O_2$, 281.1290; found, 281.1289.

3-Isopropyl-5-(3-methoxy-phenyl)-1,3-dihydro-benzo[e][1,4]-diazepin-2-one 12(13). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.53 (bs, 1H, –NH), 7.57 (td, 1H, $J = 8.79$, 1.92 Hz, arom H), 7.24–7.35 (m, 3H, arom H), 7.18 (td, 1H, $J = 8.01$, 1.14 Hz, arom H), 7.04–7.09 (m, 2H, arom H), 6.99 (d, 1H, $J = 8.04$ Hz, arom H), 3.76 (s, 3H, –OCH_3), 3.01 (d, 1H, $J = 8.91$ Hz, =N–C *H*–(C=O)–CH–), 2.47–2.52 (m, 1H, $(CH_3)_2$–C *H*–CH–), 1.11 (d, 3H, $J = 6.72$ Hz, –CH_3), 0.98 (d, 3H, $J = 6.54$ Hz, –CH_3). ^{13}C NMR ($(CD_3)_2SO$) δ: 169.39, 167.05, 158.9, 140.34, 139.07, 131.44, 130.3, 129.25, 126.26, 122.51, 121.79, 120.99, 115.50, 114.53, 68.88, 55.17, 28.90, 19.89, 18.69. HRMS (ES) *m*/*z* calcd for (M^+) $C_{19}H_{20}N_2O_2$, 309.1603; found, 309.1607.

3-Isobutyl-5-(3-methoxy-phenyl)-1,3-dihydro-benzo[e][1,4]-diazepin-2-one 12(14). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.53 (bs, 1H, –NH), 7.57 (t, 1H, $J = 7.26$ Hz, arom H), 7.34 (t, 1H, $J = 8.04$ Hz, arom H), 7.24–7.30 (m, 2H, arom H), 7.18 (td, 1H, $J = 7.26$, 0.75 Hz, arom H), 7.07 (dd, 1H, $J = 4.98$, 2.04 Hz, arom H), 6.96–7.01 (m, 2H, arom H), 3.76 (s, 3H, –OCH_3), 3.47 (dd, 1H, $J = 9.06$, 4.8 Hz, =N–C *H*–(C=O)–CH_2–), 2.02–2.09 (m, 1H, –$(CH_3)_2$–C *H*–CH_2–), 1.78–1.91 (m, 2H, –CH_2–), 0.95 (d, 3H, $J = 6.42$ Hz, –CH_3), 0.79 (d, 3H, $J = 6.24$ Hz, –CH_3). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.49, 167.35, 158.88, 140.28, 139.10, 131.49, 130.26, 129.23, 126.31, 122.53, 121.75, 120,98, 115.43, 114.59, 61.19, 55.173, 39.47, 24.20, 23.25, 21.80. HRMS (ES) *m*/*z* calcd for (M^+) $C_{20}H_{22}N_2O_2$, 323.1759; found, 323.1748.

[5-(3-Methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-3-yl]-acetic acid *tert*-butyl ester 12(15). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.65 (bs, 1H, –NH), 7.60 (td, 1H, $J = 6.9$, 1.53, arom H), 7.34 (t, 1H, $J = 7.89$ Hz, arom H), 7.26–7.30 (m, 2H, arom H), 7.21 (t, 1H, $J = 7.26$ Hz, arom H), 7.07 (d, 1H, $J = 8.4$ Hz, arom H), 7.03 (m, 1H, arom H), 6.93 (d, 1H, $J = 7.8$Hz, arom H), 3.86 (t, 1H, $J = 7.17$ Hz, –CH–), 3.75 (s, 3H, –OCH_3), 3.07 (dd, 1H, $J = 16.4$, 7.14 Hz, –CH_2–), 2.94 (dd, 1H, $J = 16.4$, 7.2 Hz, –CH_2–), 1.39, (s, 9H, –$(CH_3)_3$). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.27, 169.79, 167.78, 158.91, 139.94, 138.97, 131.68, 130.32, 129.22, 126.35, 122.73, 121.84, 121.07, 115.75, 114.41, 79.69, 60.32, 55.03, 37.14, 27.66 (3C). HRMS (ES) *m*/*z* calcd for (M^+) $C_{22}H_{24}N_2O_4$, 381.1814; found, 381.1869.

3-[5-(3-Methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]-diazepin-3-yl]-propionic acid *tert*-butyl ester 12(16). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.59 (bs, 1H, –NH), 7.57 (t, 1H, $J = 8.46$ Hz, arom H), 7.35 (t, 1H, $J = 7.92$ Hz, arom H) 7.24–7.27 (m, 2H, arom H), 7.18, (td, 1H, 7.29, 0.9 Hz, arom H), 7.08 (dd, 1H, $J = 7.5$, 2.55 Hz, arom H), 7.00–7.03 (m, 2H, arom H), 3.76 (s, 3H, –OCH_3), 3.49 (dd, 1H, $J = 7.92$, 5.94 Hz, –CH–), 2.41–2.46 (m, 2H, –CH– CH_2–CH_2–), 2.21–2.26 (m, 2H, –CH_2– CH_2–(C=O)–), 1,32 (s, 9H, –$(CH_3)_3$). ^{13}C NMR ($(CD_3)_2SO$) δ: 172.20, 170.34, 167.90, 158.89, 140.23, 139.00, 131.55, 130.31, 129.24, 126.36, 122.57, 121.81, 121.03, 115.48, 114.71, 79.37, 61.55, 55.07, 31.16, 27.59 (3C), 26.41. HRMS (ES) *m*/*z* calcd for (M^+) $C_{23}H_{26}N_2O_4$, 395.1971; found, 395.1958.

3-*tert*-Butoxymethyl-5-(3-methoxy-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(17). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.58 (bs, 1H, –NH), 7.58 (t, 1H, $J = 7.26$ Hz, arom H), 7.24–7.34 (m, 3H, arom H), 7.19 (t, 1H, $J = 6.87$ Hz, arom H), 7.06–7.09 (m, 2H, arom H), 6.97 (dd, 1H, $J = 7.62$, 1.02 Hz, arom H), 4.16 (dd, 1H, $J = 8.88$, 6.51 Hz, –CH_2–), 3.88 (dd, 1H, $J = 8.88$, 6.21 Hz, –CH_2–), 3.76 (s, 3H, –OCH_3), 3.46 (t, 1H, $J = 6.27$ Hz, –CH–), 1.20 (s, 9H, –$(CH_3)_3$). ^{13}C NMR ($(CD_3)_2SO$) δ: 169.04, 167.71, 158.93, 140.04, 138.95, 131.55, 130.30, 129.21, 126.34, 122.65, 121.86, 121.12, 115.75, 114.41, 72.48, 63.83, 61.95, 55.04, 27.17 (3C). HRMS (ES) *m*/*z* calcd for (M^+) $C_{21}H_{24}N_2O_3$, 353.1865; found, 353.1894.

7-Chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(18). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.64 (bs, 1H, –NH), 7.64, (dd, 1H, $J = 8.73$, 2.43 Hz) 7.42–7.53 (m, 5H), 7.28 (d, 1H, $J = 8.76$ Hz), 7.21 (d, 1H, $J = 2.43$), 4.17 (bs, 2H,

–CH_2–). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.07, 168.31, 138.55, 138.54, 131.21, 130.33, 129.61, 129.11 (2C), 128.27 (2C), 127.64, 126.33, 123.03, 56.92. HRMS (ES) *m/z* calcd for (M^+) $C_{15}H_{11}ClN_2O$, 271.0638; found, 271.0630.

7-Chloro-3-methyl-5-phenyl-1,3-dihydro-benzo[e][1,4]-diazepin-2-one 12(19). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.65 (bs, 1H, –NH), 7.64 (dd, 1H, J = 8.70, 2.46 Hz), 7.42–7.56 (m, 5H), 7.27 (d, 1H, J = 8.73 Hz), 7.23 (d, 1H, J = 2.43 Hz), 3.68 (q, 1H, J = 6.33 Hz, –CH–), 1.53 (d, 3H, J = 6.39 Hz, –CH_3). ^{13}C NMR ($(CD_3)_2SO$) δ: 171.03, 166.20, 138.31, 138.16, 131.40, 130.24, 129.29, 129.14 (2C), 128.25 (2C), 127.92, 126.28, 122.97, 58.51, 17.06. HRMS (ES) *m/z* calcd for (M^+) $C_{16}H_{13}ClN_2O$, 285.0794; found, 285.0789.

(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-3-yl)-acetic acid *tert*-butyl ester 12(20). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.59 (bs, 1H, –NH), 7.68 (dd, 1H, J = 8.75, 2.52 Hz), 7.45–7.55 (m, 5H), 7.31 (d, 1H, J = 8.72 Hz), 7.25 (d, 1H, J = 2.42 Hz), 3.90 (t, 1H, J = 7.04 Hz, –CH–), 3.09 (dd, 1H, J = 16.51, 7.45 Hz, –CH_2–), 2.94 (dd, 1H, J = 16.49, 6.88 Hz, –CH_2–), 1.40 (s, 9H, –$(CH_3)_3$). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.17, 169.56, 166.85, 138.06, 131.70, 130.47, 129.36, 129.17 (2C), 128.40, 128.31 (2C), 127.78, 126.60, 123.10, 79.80, 60.46, 31.18, 27.67 (3C). HRMS (ES) *m/z* calcd for (M^+) $C_{21}H_{21}ClN_2O_3$, 385.1319; found, 385.1349.

3-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-3-yl)-propionic acid *tert*-butyl ester 12(21). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.71 (bs, 1H, –NH), 7.65 (dd, 1H, J = 8.73, 2.5 Hz), 7.45–7.56 (m, 5H), 7.28 (d, 1H, J = 8.75 Hz), 7.21 (d, 1H, J = 2.41 Hz), 3.54 (dd, 1H, J = 7.94, 5.77 Hz, –CH–), 2.39–2.46 (m, 2H, –CH– *CH_2*–CH_2–), 2.26 (m, 2H, –CH_2– *CH_2*–(C=O)–), 1.35 (s, 9H, –$(CH_3)_3$). ^{13}C NMR ($(CD_3)_2SO$) δ: 172.19, 170.17, 166.87, 138.31, 138.10, 131.51, 130.39, 129.22, 129.10 (2C), 128.28 (2C), 128.82, 126.40, 123.08, 79.41, 61.77, 31.17, 27.62 (3C), 26.38. HRMS (ES) *m/z* calcd for (M^+) $C_{22}H_{23}ClN_2O3$, 399.1475; found, 399.1510.

3-*tert*-Butoxymethyl-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(22). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.69 (bs, 1H, –NH), 7.66 (dd, 1H, J = 8.73, 2.4 Hz), 7.45–7.52 (m, 5H), 7.28 (d, 1H, J = 8.76 Hz), 7.26, (d, 1H, J = 2.46 Hz), 4.16 (dd, 1H, J = 8.88, 6.54 Hz, –CH_2–), 3.88 (dd, 1H, J = 8.91, 6.15 Hz, –CH_2–), 3.51 (t, 1H, J = 6.3 Hz, –CH–), 1.20 (s, 9H, –$(CH_3)_3$). ^{13}C NMR ($(CD_3)_2SO$) δ: 168.89, 166.88, 128.27, 138.09, 131.61, 130.48, 129.48, 129.28 (2C), 128.38 (2C), 127.87, 126.60, 123.22, 72.62, 64.05, 61.97, 27.45 (3C). HRMS (ES) *m/z* calcd for (M^+) $C_{20}H_{21}ClN_2O_2$, 357.1370; found, 357.1393.

3-Benzyl-5-thiophen-2-yl-1,3-dihydro-benzo[e][1,4]-diazepin-2-one 12(23). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.58 (bs, 1H, –NH), 7.71 (dd, 1H, J = 4.92, 1.29 Hz, arom H), 7.60 (m, 2H, arom H), 7.30 (d, 2H, J = 7.05 Hz, arom H), 7.20–7.25 (m, 4H, arom H), 7.07–7.14 (m, 3H, arom H), 3.65 (dd, 1H, J = 8.25, 5.34 Hz, –CH–), 3.22–3.37 (m, 2H, –CH_2–). ^{13}C NMR ($(CD_3)_2SO$) δ: 179.86, 161.93, 144.23, 139.58, 139.04, 132.21, 131.26, 130.97, 130.24, 130.07 (2C), 128.35 (2C), 128.19, 126.33, 127.07, 123.48, 121.70, 64.79, 29.38. HRMS (ES) *m/z* calcd for (M^+) $C_{20}H_{16}N_2OS$, 333.1061; found, 333.1044.

3-Benzyl-7-chloro-5-(3-methoxy-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(24). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.70 (bs, 1H, –NH), 7.63 (dd, 1H, J = 8.76, 2.43 Hz, arom H), 7.18–7.36 (m, 8H, arom H), 7.08 (dd, 1H, J = 8.4, 2.67 Hz, arom H), 6.99 (d, 1H, J = 2.4 Hz, arom H), 6.88 (d, 1H, J = 8.04 Hz, arom H), 3.77, (s, 3H, –OCH_3), 3.72 (t, 1H, J = 6.87Hz, –CH–), 3.32 (m, 2H, –CH_2–). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.02, 166.21, 159.00, 139.74, 139.09, 138.13, 131.63 (2C), 129.77, 129.48, 128.32, 127.95 (2C), 127.62, 126.43, 125.98, 123.11, 121.83, 116.21, 114.16, 64.69, 55.29, 36.99. HRMS (ES) *m/z* calcd for (M^+) $C_{23}H_{19}ClN_2O_2$, 391.1213; found, 391.1222.

5-Naphthalen-2-yl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(25). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.58 (s, 1H, –NH), 7.97 (d, 3H, J = 8.79 Hz, arom H), 7.92 (s, 1H, arom H), 7.73 (dd, 1H, J = 8.79, 1.92 Hz, arom H), 7.54–7.63 (m, 3H, arom H), 7.34 (d, 1H, J = 1.53 Hz, arom H), 7.30 (dd, 1H, J = 10.32, 1.53 Hz, arom H), 7.20 (td, 1H, J =8.4, 1.14 Hz, arom H), 4.19 (s, 2H, –CH_2–). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.37, 169.53, 139.60, 136.47, 133.55, 132.14, 131.55, 130.68, 129.50, 128.68, 127.70, 127.42, 127.22, 126.50, 126.30, 126.09, 122.70, 121.09, 57.04. HRMS (ES) *m/z* calcd for (M^+) $C_{19}H_{14}N_2O$, 287.1184; found, 287.1170.

5-Naphthalen-2-yl-8-trifluoromethyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(26). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.80 (s, 1H, –NH), 7.99 (d, 3H, J = 8.4 Hz, arom H), 7.94 (d, 1H, J = 1.14 Hz, arom H), 7.76 (dd, 1H, J = 8.4, 1.53 Hz, arom H), 7.63 (s, 1H, arom H), 7.54–7.61 (m, 4H, arom H), 4.27 (s, 2H, –CH_2–). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.36, 168.67, 140.20, 135.91, 133.64, 132.29, 132.18, 129.69, 129.59, 128.77, 127.87, 127.43, 126.57, 125.93, 118.95, 118.91, 117.91, 117.86, 57.03. HRMS (ES) *m/z* calcd for (M^+) $C_{20}H_{13}F_3N_2O$, 355.1058; found, 355.1076.

7-Chloro-9-fluoro-5-(3,4-methyl-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(27). ^{1}H NMR ($(CD_3)_2SO$) δ: 10.48 (s, 1H, –NH), 7.76 (dd, 1H, J = 9.93, 2.28 Hz, arom H), 7.36 (s, 1H, arom H), 7.18–7.20 (m, 2H, arom H), 7.06 (t, 1H, J =1.92 Hz, arom H), 4.16 (bs, 2H, –CH_2–), 2.27 (s, 3H, –CH_3), 2.25 (s, 3H, –CH_3). ^{13}C NMR ($(CD_3)_2SO$) δ: 169.58, 167.32, 139.17, 136.30, 135.74, 130.20, 129.88, 129.32, 126.79, 126.65, 125.39, 125.35, 118.05, 117.75, 56.82, 19.24, 19.20. HRMS (ES) *m/z* calcd for (M^+) $C_{17}H_{14}ClFN_2O$, 317.0857; found, 317.0850.

Representative Procedure for Catch of 2-Aminobenzoimines 4 on Amino Acid Resins 10 on Large Scale. Fmoc-protected Wang resin **9** (2.8 g, 2.2 mmol) was deprotected by treating it with 16 mL of DMF and 4 mL of piperidine for 30 min. The resin was washed repeatedly with DMF using suction filtration. 2-Aminobenzoimine **4** (13 mmol) was prepared according to Scheme 1, dissolved in 20 mL of NMP and added to the resin. The reaction was stirred for 30 min at 120 °C in a microwave oven and the resin was washed with DCM using suction filtration until the washings were no longer colored.

Cleavage from the Resin 11 Giving 1,4-Benzodiazepine-2-ones 12 on Large Scale (12(18), 12(28)). The resin was transferred to a 20 mL syringe fitted with a filter and tap, and treated with 15 mL of cleavage mixture (50%

AcOH/50% DCE) for 16 h. After draining the syringe, the resin was washed with 2 × 5 mL of DCM. The reaction filtrate and washings were evaporated. To remove traces of AcOH, the residue was dissolved in DCM/hexane 1:1 mixture, evaporated, and freeze dried which gave pure product **12** as a pale yellow solid. Yield: 56–65 %.

[4-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]-diazepin-3-yl)-butyl]-carbamic acid *tert*-butyl ester 12(28). ^{1}H NMR (CD_3OD) δ: 7.57 (dd, 1H, J = 8.73, 2.37 Hz), 7.44–7.50 (m, 5H), 7.25 (d, 1H, J = 8.76 Hz), 7.22 (d, 1H, J = 2.4 Hz), 3.54 (dd, 1H, J = 8.03, 5.92 Hz, –CH–), 3.07 (t, 2H, J = 6.59 Hz, –CH_2– *CH_2*–NH–), 2.14–2.18 (m, 2H, –CH_2–), 1.52–1.58 (m, 4H, –CH_2–CH_2–), 1.41 (s, 9H, –$(CH_3)_3$). ^{13}C NMR (CD_3OD) δ: 172.77, 170.66, 158.62, 140.12, 139.40, 133.23, 131.91, 131.50, 130.84 (2C), 130.14, 129.58, 129.56 (2C), 124.06, 79.84, 64.64, 41.31, 31.58, 30.96, 28.84 (3C), 24.37. HRMS (ES) *m*/*z* calcd for (M^+) $C_{24}H_{28}ClN_3O_3$, 442.1897; found ,442.1916.

7-Chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 12(18). ^{1}H NMR (CD_3OD) δ: 7.58 (dd, 1H, J = 8.73, 2.4 Hz), 7.44–7.53 (m, 5H, arom H 4,5,6,7,8), 7.25 (d, 1H, J = 8.73 Hz), 7.22 (d, 1H, J = 2.43 Hz), 4.24 (bs, 2H, –CH_2–). ^{13}C NMR (CD_3OD) δ: 172.52, 172.43, 140.14, 139.73, 133.3, 132.00, 131.82, 130.71 (2C), 129.79 (2C), 129.66, 129.61, 124.12, 57.63. HRMS (ES) *m*/*z* calcd for (M^+) $C_{15}H_{11}ClN_2O$, 271.0638; found, 271.0634.

Representative Procedure for Alkylation of 1,3-Dihydro-1,4-benzodiazepine-2-ones 12. BEMP resin (186 mg, 0.4 mmol) was weighed out into the MiniBlock. 1,3-dihydro-1,4-benzodiazepine-2-one **12** (0.14 mmol) prepared according to the described procedure was dissolved in 2 mL of DMF and added to the resin. After 30 min on the Bohdan Shaker the alkylating agent **13** (0.28 mmol) was added and the reactions were shaken for a further 4 h. Draining the resin and evaporation of the solvent gave the products **14** which in all cases, except for one, needed HPLC purification. Yields: 18–71%.

7-Chloro-1-methyl-5-phenyl-1,3-dihydro-benzo[e][1,4]-diazepin-2-one 14(1). ^{1}H NMR ($(CD_3)_2SO$) δ: 7.72 (dd, 1H, J = 8.87, 2.56 Hz), 7.62 (d, 1H, J = 8.90 Hz), 7.44–7.57 (m, 5H, arom H 4,5,6,7,8), 7.22 (d, 1H, J = 2.51 Hz), 4.59 (d, 1H, J = 10.72 Hz, –CH_2–), 3.79 (d, 1H, J = 10.72 Hz, –CH_2–), 3.31 (s, 3H, –CH_3). ^{13}C NMR ($(CD_3)_2SO$) δ: 169.52, 168.39, 142.93, 138.30, 131.76, 130.94, 129.82, 129.49 (2C), 129.21, 128.75 (2C), 128.09, 124.19, 57.04, 34.63. HRMS (ES) *m*/*z* calcd for (M^+) $C_{16}H_{13}ClN_2O$, 285.0794; found, 285.0776.

[4-(7-Chloro-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-butyl]-carbamic acid *tert*-butyl ester 14(2). ^{1}H NMR ($(CD_3)_2SO$) δ: 7.72 (dd, 1H, J = 8.90, 2.51 Hz), 7.62 (d, 1H, J = 8.90 Hz), 7.43–7.58 (m, 5H), 7.24 (d, 1H, J = 2.45 Hz), 6.74 (bs, 1H, –(C=O)–NH–), 3.48 (dd, 1H, J = 8.01, 5.68 Hz, –CH–), 2.93 (t, 2H, J = 6.34 Hz, –CH_2– *CH_2*–NH–), 1.20–2.08 (m, 2H, –CH_2–), 1.30–1.43 (m, 4H, –CH_2–CH_2–), 1.35, (s, 9H, –$(CH_3)_3$). ^{13}C NMR ($(CD_3)_2SO$) δ: 170.05, 166.51, 155.90, 142.61, 138.21, 131.78, 130.89, 130.12, 129.54 (2C), 128.91, 128.73 (2C), 128.08, 124.37, 77.61, 63.30, 34.93, 31.38, 29.92, 28.60 (3C), 23.16. HRMS (ES) *m*/*z* calcd for (M^+) $C_{25}H_{30}ClN_3O_3$, 456.2054; found, 456.2053.

1-Allyl-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]-diazepin-2-one 14(3). ^{1}H NMR ($(CD_3)_2SO$) δ: 7.70 (dd, 1H, J = 8.91, 2.4 Hz), 7.64 (d, 1H, J = 8.88 Hz), 7.45–7.56 (m, 5H), 7.22 (d, 1H, J = 2.34 Hz), 5.72 (m, 1H, –C *H*=CH_2), 5.07 (dd, 1H, J = 10.68, 1.53 Hz, –CH= *CH_2* (cis)), 5.02 (dd, 1H, J = 17.52, 1.89 Hz, –CH= *CH_2*(trans)), 4.66 (dd, 1H, J= 15.00, 4.65 Hz, –N–CH_2–), 4.61 (d, 1H, J = 10.53 Hz, –C=N–CH_2–(C=O)–), 4.42 (dd, 1H, J = 16.53, 5.55 Hz, –N–CH_2–), 3.85 (d, 1H, J = 10.5, C=N–CH_2–(C=O)–). ^{13}C NMR ($(CD_3)_2SO$) δ: 168.13, 168.03, 141.13, 137.87, 133.12, 131.33, 130.53, 130.46, 128.93 (2C), 128.80, 128.41 (2C), 128.08, 124.33, 116.59, 56.65, 48.17. HRMS (ES) *m*/*z* calcd for (M^+) $C_{18}H_{15}ClN_2O$, 311.0951; found, 311.0951.

7-Chloro-1-(2-cyclohexyl-ethyl)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 14(4). ^{1}H NMR ($(CD_3)_2SO$) δ: 7.71 (d, 2H, J = 1.35 Hz), 7.43–7.58 (m, 5H), 7.25 (d, 1H, J = 1.37 Hz), 4.56 (d, 1H, J = 10.50 Hz, –C=N–CH_2–(C=O)–), 4.37 (dt, 1H, J = 14.09, 7.2 Hz, –N– *CH_2*–CH_2–), 3.77 (d, 1H, J = 10.52 Hz, –C=N– *CH_2*–(C=O)–), 3.66 (dt, 1H, J = 14.10, 5.81 Hz, –N– *CH_2*–CH_2–), 1.35–1.56 (m, 5H, aliphatic H), 1.22 (q, 2H, J = 6.57 Hz, aliphatic H), 0.64–0.96 (m, 6H, aliphatic H). ^{13}C NMR ($(CD_3)_2SO$) δ: 168.28, 167.45, 140.42, 137.38, 131.11, 130.78, 130.38, 128.64 (2C), 128.57, 128.17 (2C), 128.02, 124.59, 56.59, 41.90, 34.14, 33.44, 32.62, 31.75, 25.56, 25.15, 25.11. HRMS (ES) *m*/*z* calcd for (M^+) $C_{23}H_{25}ClN_2O$, 381.1733; found, 381.1708.

7-Chloro-1-(5-iodo-pentyl)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 14(5). ^{1}H NMR ($(CD_3)_2SO$) δ: 7.71 (d, 2H, J = 1.35 Hz), 7.44–7.57 (m, 5H), 7.24 (d, 1H, J = 1.11 Hz), 4.56 (d, 1H, J = 10.5 Hz, –C=N– *CH_2*–(C=O)–), 4.25 (dt, 1H, J = 14.01, 7.41 Hz, –N– *CH_2*–CH_2–), 3.78 (d, 1H, J = 10.53 Hz, –C=N– *CH_2*–(C=O)–), 3.67 (dt, 1H, J = 14.01, 6.9 Hz, –N– *CH_2*–CH_2–), 2.96 (td, 2H, J = 7.02, 3.15 Hz, –CH_2– *CH_2*–I), 1.51–1.60 (m, 2H, – *CH_2*–CH_2–I), 1.41–1.44 (m, 1H, –N–CH_2– *CH_2*–), 1.30 (m, 1H, –N–CH_2– *CH_2*–), 1.00–1.08 (m, 2H, – *CH_2*–CH_2–CH_2–I). ^{13}C NMR ($(CD_3)_2SO$) δ: 168.40, 167.80, 140.72, 137.69, 131.37, 130.91, 130.55, 128.87 (2C), 128.75, 128.38 (2C), 128.24, 124.81, 56.76, 44.77, 32.28, 26.69, 25.96, 7.83. HRMS (ES) *m*/*z* calcd for (M^+) $C_{20}H_{20}ClIN_2O$, 467.0387; found, 467.0422.

7-Chloro-1-phenethyl-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 14(6). ^{1}H NMR ($(CD_3)_2SO$) δ: 7.76 (d, 1H, J = 8.90 Hz), 7.70 (dd, 1H, J = 8.90, 2.43 Hz), 7.45–7.54 (m, 5H, arom H), 7.18 (d, 1H, J = 2.37 Hz), 7.02–7.07 (m, 5H, arom H), 4.55 (d, 1H, J = 10.61 Hz, –C=N– *CH_2*–(C=O)–), 4.48 (dt, 1H, J =14.03, 7.46 Hz, –N– *CH_2*–CH_2–), 3.95 (dt, 1H, J = 13.95, 6.81 Hz, –N–*CH_2*–CH_2–), 3.75 (d, 1H, J = 10.58 Hz, –C=N– *CH_2*–(C=O)–), 2.72–2.80 (m, 1H, – *CH_2*–Ar), 2.62–2.69 (m, 1H, – *CH_2*–Ar). ^{13}C NMR ($(CD_3)_2SO$) δ: 168.49, 167.77, 140.82, 137.98, 137.56, 131.32, 130.68, 130.42, 129.01 (2C), 128.82, 128.31, 128.22 (2C), 128.09 (2C), 128.02 (2C), 126.07, 124.59, 56.70, 46.47, 33.05. HRMS (ES) *m*/*z* calcd for (M^+) $C_{23}H_{19}ClN_2O$, 375.1264; found, 375.1272.

7-Chloro-1-(3-methyl-but-2-enyl)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 14(7). ^{1}H NMR ($(CD_3)_2SO$) δ: 7.70 (dd, 1H, J = 8.85, 2.34 Hz), 7.64 (d, 1H, J = 8.85

Hz), 7.44–7.55 (m, 5H), 7.19 (d, 1H, $J = 2.31$ Hz), 4.99 (t, 1H, $J = 6.09$ Hz, –CH=), 4.66 (dd, 1H, $J = 15.27$, 6.45 Hz, –N–CH_2–), 4.57 (d, 1H, $J = 10.56$ Hz, =N–CH_2–(C=O)), 4.31 (dd, 1H, $J = 15.27$, 6.96 Hz, –N–CH_2–), 3.79 (d, 1H, $J = 10.5$ Hz, =N–CH_2–(C=O)–), 1.54 (d, 6H, $J = 12.63$ Hz, $C(CH_3)$). ^{13}C NMR ($(CD_3)_2SO$) δ: 167.97, 167.85, 141.11, 138.02, 136.01, 131.23, 130.81, 130.47, 128.79 (2C), 128.57, 128.38 (2C), 128.17, 124.71, 119.42, 56.67, 43.87, 25.14, 17.68. HRMS (ES) *m/z* calcd for (M^+) $C_{20}H_{19}ClN_2O$, 339.1264; found, 339.1268.

(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-benzo[e][1,4]-diazepin-1-yl)-acetic acid *tert*-butyl ester 14(8). ^{1}H NMR ($(CD_3)_2SO$) δ: 7.72 (dd, 1H, $J = 8.87$ Hz), 7.44–7.58 (m, 6H), 7.22 (d, 1H, $J = 2.45$ Hz), 4.62 (d, 1H, $J = 10.87$ Hz, –C=N–*CH_2*–(C=O)–), 4.51 (d, 1H, $J = 16.92$ Hz, –N–CH_2–(COO)–), 4.45 (d, 1H, $J = 17.33$ Hz, –N–CH_2–(COO)–), 3.84 (d, 1H, $J = 10.69$ Hz, –C=N– *CH_2*–(C=O)–), 1.34 (s, 9H, *t*-Bu). ^{13}C NMR ($(CD_3)_2SO$) δ: 168.82, 168.68, 167.83, 141.64, 138.32, 131.76, 130.84, 130.41, 129.71 (2C), 129.42, 129.16, 128.62 (2C), 124.33, 81.92, 56.40, 49.99, 27.84 (3C). HRMS (ES) *m/z* calcd for (M^+) $C_{21}H_{21}ClN_2O_3$, 385.1319; found, 385.1325.

7-Chloro-1-(3-chloro-propyl)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 14(9). ^{1}H NMR ($(CD_3)_2SO$) δ: 7.72 (d, 2H, $J = 2.13$ Hz), 7.45–7.57 (m, 5H), 7.22 (dd, 1H, $J = 1.77$, 0.45 Hz), 4.57 (d, 1H, $J = 10.62$ Hz, =N–CH_2–(C=O)–), 4.35 (dt, 1H, $J = 14.1$, 7.02 Hz, –N–CH_2–), 3.80 (d, 1H, $J = 13.05$ Hz, =N–CH_2–(C=O)–), 3.75–3.84 (m, 1H, –N–CH_2–), 3.30–3.48 (m, 2H, –*CH_2*–CH_2–Cl), 1.92 (m, 1H, –CH_2–Cl), 1.77 (m, 1H, –CH_2–Cl). ^{13}C NMR ($(CD_3)_2SO$) δ: 168.63, 167.96, 140.91, 137.76, 131.48, 130.79, 130.59, 128.85, 128.78 (2C), 128.45, 128.37 (2C), 124.76, 56.75, 43.34, 42.09, 30.04. HRMS (ES) *m/z* calcd for (M^+) $C_{18}H_{16}Cl_2N_2O$, 347.0718; found, 347.0709.

3-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-benzo[e][1,4]-diazepin-1-yl)-propionitrile 14(10). ^{1}H NMR ($(CD_3)_2SO$) δ: 7.73 (d, 2H, $J = 1.35$ Hz), 7.42–7.61 (m, 5H), 7.19 (d, 1H, $J = 1.32$ Hz), 4.60 (d, 1H, $J = 10.68$ Hz, =N–CH_2–(C=O)–), 4.43 (dt, 1H, $J = 14.22$, 6.39 Hz, –N–CH_2–), 3.98 (dt, 1H, $J = 14.22$, 6.36 Hz, –N–CH_2–), 3.80 (d, 1H, $J = 10.68$ Hz, =N–CH_2–(C=O)–), 2.71 (t, 2H, $J = 6.42$ Hz, –CH_2–CN). ^{13}C NMR ($(CD_3)_2SO$) δ: 168.56, 168.30, 140.33, 137.91, 131.46, 131.15, 130.42, 129.19 (2C), 128.96, 128.56, 128.16 (2C), 124.73, 118.18, 56.43, 41.89, 15.95. HRMS (ES) *m/z* calcd for (M^+) $C_{18}H_{14}ClN_3O$, 324.0903; found, 324.0892.

Titration of Grignard reagents using Diphenyl Ditelluride. A 10 mL microwave tube containing a magnetic stirring bar was heated under vacuum and cooled to room temperature under argon flow. Diphenyl ditelluride (~0.2 mmol) was added to the tube, which then was sealed with an aluminium crimp cap fitted with a silicon septum. The tube was flushed with argon, and dry THF (4 mL) was added. While stirring the tube was cooled to 0 °C in an ice bath. The Grignard reagent was added dropwise via a 1 mL syringe. When the solution turned pale yellow the amount consumed contained 1 equiv of Grignard reagent relative to diphenyl ditelluride.

Titration of Lithium reagents using *N*-Pivaloyl- *o*-toluidineb. A 10 mL microwave tube containing a magnetic stirring bar was heated under vacuum and cooled to room temperature under argon flow. *N*-Pivaloyl- *o*-toluidine (~0.4 mmol) was added and the tube was then sealed with an aluminium crimp cap fitted with a silicon septum. After flushing the tube with argon, dry THF (4 mL) was added and stirring was started. The Lithium reagent was added dropwise via a 1 mL syringe. When the solution went from colorless to intense yellow the amount consumed contained ½ equiv of Lithium reagent relative to *N*-Pivaloyl-*o*-toluidine.

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Supporting Information Available. ^{1}H- and ^{13}C-NMR spectra for benzodiazepines **12** and N-alkylated benzodiazepines **14** are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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