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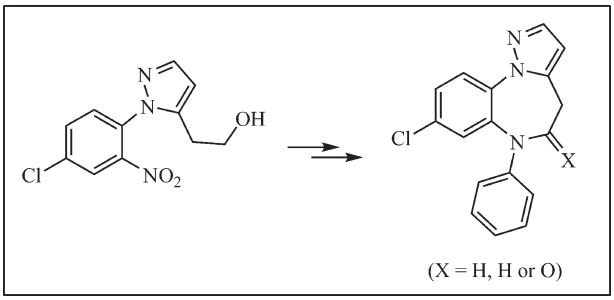


The synthesis and *in vitro* biological evaluation of two novel benzodiazepine derivatives are described. The compounds were synthesized divergently from the key amino alcohol **5**, which was realized using the unusual Weinreb-enamino ketone **10**.

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## INTRODUCTION

The medicinal chemistry literature is replete with benzodiazepine derivatives, $GABA_A$ agonists that have been used for decades [1] as sedatives, hypnotics, anxiolytics, muscle relaxers, and anticonvulsants [2]. Their widespread use is attributed to potent activity coupled with a lack of respiratory side effects, a problem associated with barbiturate predecessors [2]. Fused heterocyclic benzodiazepines such as **1** [3] (Fig. 1) have been extensively used as anxiolytics, but can have poor side effect profiles such as impairing effects on cognitive and psychomotor performance [4]. Less common are the 1,5-benzodiazepines such as compound **2**, which are less potent but have the advantage of vastly improved side effect profiles [5]. A benzodiazepine core which includes a fused heterocycle and the 1,5-nitrogen orientation may show both potency and reduced off-target issues displayed by the parent scaffolds, respectively.

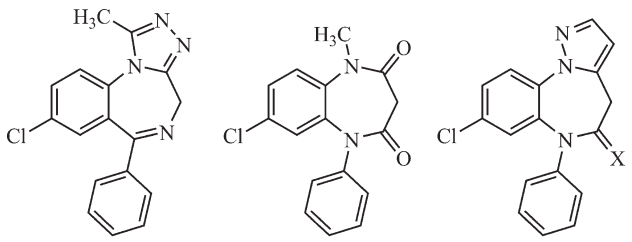
To test the accessibility of the proposed scaffolds, compounds **3** and **4** were targeted based on their homology with compounds **1** and **2**. There are no reports of structures related to compound **3**, although triazole derivatives are known [2(c),3(b)]. Structures such as compound **4** have been claimed as PAF-antagonists, but their synthesis was not reported [6]. Pyrazolo-1,4-benzodiazepines appeared in a few reports from Hoffmann–La Roche [7], but a search of the literature uncovered no current uses of the structures. Herein, we report the synthesis and $GABA_A$ binding results of a novel class of benzo[*b*]pyrazolo[1,5]diazepines (compounds **3** and **4**).

## RESULTS AND DISCUSSION

A retrosynthetic analysis reveals that compounds **3** and **4** can be accessed using amino alcohol **5** *via* an intramolecular cyclization reaction [8,9] (Scheme 1). Compound **5** can be obtained through a condensation reaction between the appropriate phenylhydrazine and acetylenic ketone **6** [10].

The attempted synthesis of intermediate **6** is shown in Scheme 2. Jones oxidation [11] of commercially available **7** followed by standard HOBt/EDCI coupling conditions afforded Weinreb amide **9**. Treatment of **9** with ethynylmagnesium bromide gave a mixture of the unexpected enamino ketone **10** [12] and the expected alkyne **6**. It was found that the ratio of **6/10** could be varied based on the temperature and duration of the workup, with longer exposures to saturated aqueous ammonium chloride at 50°C affording **10** exclusively. Although it was difficult to isolate **6** in acceptable yield, compound **10** was recognized as a suitable alternative as enamino ketones are commonly used as precursors in heterocycle formations [12(c),13].

The synthesis of cyclization precursor **5** is shown in Scheme 3. A diazotization and reduction sequence [14] afforded hydrazine hydrochloride **12**, which was condensed with enamino ketone **10** to afford 5-substituted pyrazole **13a** as the major product. The alternate regioisomer (compound **13b**) was readily separated by column chromatography and both structures were confirmed by one-dimensional (1D) NOE experiments. A global deprotection of **13a** *via* hydrogenation afforded the key intermediate amino alcohol **5**.




**1** alprazolam (Xanax) **2** clobazam (Urbanol) **3** (X = H, H) **4** (X = O)

**Figure 1.** Structures of known fused heterocyclic benzodiazepine (compound **1**), known [1,5]benzodiazepine (compound **2**), and proposed fused heterocyclic [1,5]benzodiazepines (compounds **3** and **4**).

Initially, an iridium-catalyzed one-step cyclization procedure [8] was attempted to prepare **14**, but the conditions attempted (conditions a and b, Scheme 4) failed to provide acceptable yields. Alternatively, the two-step chlorination/cyclization of **5** with thionyl chloride/NMP [15] afforded **14** in excellent yield (condition c, Scheme 4).

Although the reaction of **14** with benzyne gave the highest yield of **3** (condition a, Scheme 5) [16], a more general palladium, catalyzed coupling reaction between **14** and halobenzene was desired. A survey of a variety of coupling conditions was performed, yielding modest results (conditions b–f, Scheme 5) [17].

The synthesis of lactam **15** using a rhodium-catalyzed oxidative cyclization [9] is shown in Scheme 6. The literature conditions afforded a poor yield of **15** along with unreacted starting material (condition a, Scheme 6). Extending the reaction time (condition b, Scheme 6) afforded an improved yield when the temperature is increased (conditions c and d). *N*-Arylation of **15** with phenyl iodide under standard Buchwald coupling conditions [18] afforded the desired target **4** in moderate yield.

Analogs **3** and **4** were evaluated in a specific binding assay of $GABA_A$ [19] receptors, which are responsible for the majority of neuronal inhibition in the mammalian CNS [20]. We were surprised to find that in spite of the homology with known $GABA_A$ agonists, no noticeable binding was observed from either compound. However, we envision our method to be applicable to the preparation of a variety of related diazepine derivatives to target $GABA_A$ agonism (or other biological targets), which will be reported in due course.

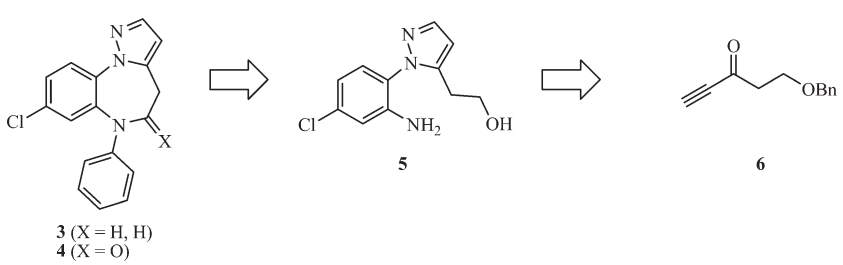
In conclusion, we have synthesized two novel benzo[*b*]pyrazolo[1,5]diazepine derivatives. The key intermediate amino alcohol **5** was prepared in six overall steps. Divergent cyclization of the key intermediate followed by standard coupling conditions readily afforded the two desired targets.

## EXPERIMENTAL

**3-(Benzyloxy)propanoic acid (8).** A mixture of 3-(benzyloxy)propan-1-ol (30.0 g, 180 mmol) in acetone (920 mL) at 0°C was treated dropwise with Jones reagent over a period of 30 min. After the addition was complete, the mixture was stirred at 0°C for 2.25 h then allowed to warm to ambient temperature over a period of 30 min. After this time, the reaction was filtered through diatomaceous earth and the filtrate was concentrated under reduced pressure. The residue obtained was diluted with ethyl acetate (450 mL), washed with water (400 mL), dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The residue obtained was diluted with methylene chloride (500 mL) then extracted with 2*M* aqueous sodium hydroxide (2 × 300 mL). The aqueous extracts were combined, washed with methylene chloride (2 × 400 mL), acidified with concentrated hydrochloric acid (pH ~1), and then extracted with chloroform (2 × 400 mL). The organic layer was dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to afford 3-(benzyloxy)propanoic acid (25.4 g, 78%) as yellow oil: $^1$H NMR (300 MHz, $CDCl_3$): δ 7.36–7.29 (m, 5H), 4.56 (s, 2H), 3.76 (t, $J$ = 6.0 Hz, 1H), 2.68 (t, $J$ = 6.3 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 176.9, 137.8, 128.4, 127.8, 127.7, 73.2, 65.2, 34.9; HRMS (TOF, $ES^+$) $m/z$ $[M + H]^+$ calcd for $C_{10}H_{13}O_3$: 181.0865; found: 181.0871.

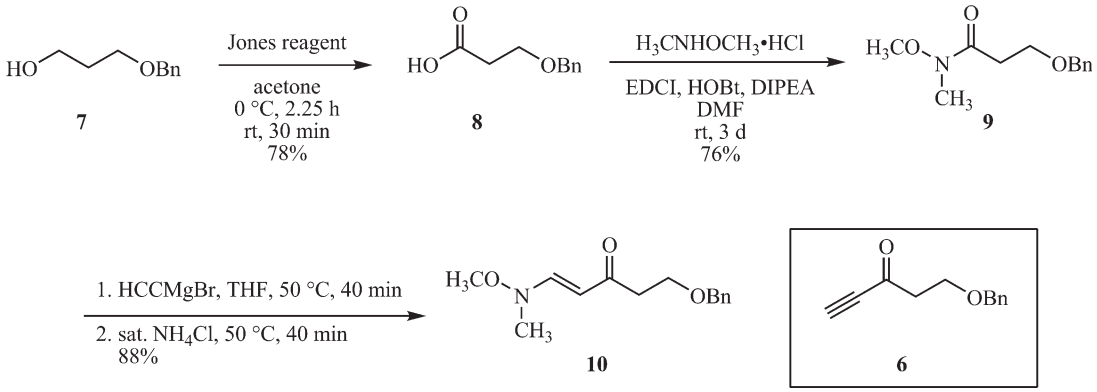
**3-(Benzyloxy)-*N*-methoxy-*N*-methylpropanamide (9).** A mixture of 3-(benzyloxy)propanoic acid (25.4 g, 141 mmol), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (32.4 g, 169 mmol), 1-hydroxybenzotriazole (22.9 g, 169 mmol), *N*,*N*-diisopropylethylamine (54.7 g, 423 mmol), and *N*,*O*-dimethylhydroxylamine hydrochloride (16.5 g, 169 mmol) in DMF (125 mL) was stirred at ambient temperature for 3 days. After this time, the reaction was poured into water (1 L) and extracted with ethyl acetate (2 × 750 mL). The combined organic extracts were washed with water (1 L) then 5% aqueous lithium chloride (2 × 1 L), dried over sodium sulfate,

**Scheme 1**




**3** (X = H, H) **4** (X = O) **5** **6**

**Scheme 2**

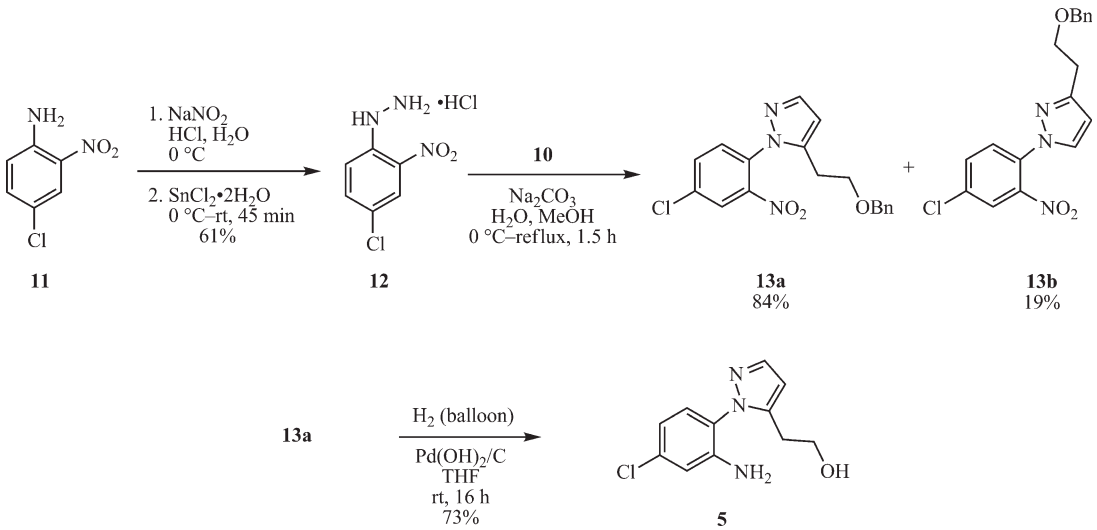



filtered, and the filtrate was concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, heptane to 1:1 ethyl acetate/heptane) to afford 3-(benzyloxy)-*N*-methoxy-*N*-methylpropanamide (23.9 g, 76%) as clear colorless liquid: $^1$H NMR (500 MHz, $CDCl_3$): δ 7.34–7.31 (m, 4H), 7.30–7.25 (m, 1H), 4.55 (s, 2H), 3.83–3.79 (m, 2H), 3.68 (s, 3H), 3.19 (s, 3H), 2.76 (t, $J$ = 6.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 172.3, 138.3, 128.4, 127.7, 127.6, 73.3, 65.9, 61.3, 32.5, 32.1; HRMS (TOF, ES$^+$) *m/z* [M + H]$^+$ calcd for $C_{12}H_{18}NO_3$: 224.1287; found: 224.1280.

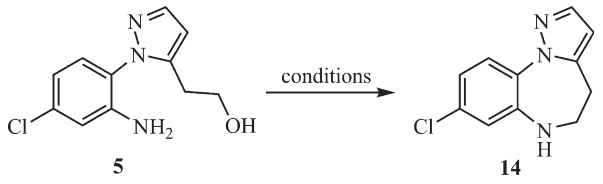
**5-(Benzyloxy)-1-(methoxy(methyl)amino)pent-1-en-3-one (10).** A solution of 0.5*M* ethynylmagnesium bromide in THF (268 mL, 134 mmol) was added to 3-(benzyloxy)-*N*-methoxy-*N*-methylpropanamide (23.9 g, 107 mmol) then the mixture was heated at 50°C for 40 min. The reaction was cooled to ambient temperature, treated with saturated aqueous ammonium chloride (220 mL), and then heated at 50°C for 40 min. After this time, the reaction was cooled to ambient temperature, extracted with ethyl acetate (800 mL), washed with brine (800 mL), dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, heptane to 7:3 ethyl acetate/heptane) to afford 5-(benzyloxy)-1-(methoxy(methyl)amino)pent-1-en-3-one (23.5 g, 88%) as orange liquid: $^1$H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, $J$ = 13.0 Hz, 1H), 7.33–7.25 (m, 5H), 5.45 (d, $J$ = 12.5 Hz, 1H), 4.53 (s, 2H), 3.79 (t, $J$ = 6.5 Hz, 2H), 3.65 (s, 3H), 3.11 (s, 3H), 2.71 (t, $J$ = 6.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 196.3, 147.9, 138.4, 128.3, 127.7, 127.5, 98.3, 73.1, 66.6, 59.9, 41.8, 39.7; HRMS (TOF, ES$^+$) *m/z* [M + H]$^+$ calcd for $C_{14}H_{20}NO_3$: 250.1443; found: 250.1433.

**(4-Chloro-2-nitrophenyl)hydrazine hydrochloride (12).** A mixture of concentrated hydrochloric acid (381 mL) and 4-chloro-2-nitroaniline (50.0 g, 290 mmol) was treated with a solution of sodium nitrite (20.0 g, 290 mmol) in water (190 mL) dropwise at a rate such that the internal temperature was maintained below 10°C. The resultant mixture was poured into a solution of tin(II) chloride dihydrate (131 g, 579 mmol) in concentrated hydrochloric acid (141 mL) at 0°C and the resultant mixture was stirred at 0°C for 3 min then allowed to warm to ambient temperature over a period of 45 min. After this time, the solid that formed was collected by filtration and recrystallized from 2-propanol to afford (4-chloro-2-nitrophenyl)hydrazine hydrochloride (39.3 g, 61%) as yellow solid: mp 188–194°C; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 9.29 (m, 4H), 8.14 (d, $J$ = 2.5 Hz, 1H), 7.81 (dd, $J$ = 9.5, 2.5 Hz, 1H), 7.41

**Scheme 3**



**Scheme 4.** Conditions: (a) $[Cl_2IrCp(CH_3)_5]_2$, $K_2CO_3$, toluene, 111°C, 19 h, 23%; (b) $[Cl_2IrCp(CH_3)_5]_2$, $K_2PO_4$, toluene, 111°C, 18 h; 120°C, 1 h, 25%; (c) (1) $SOCl_2$, 1,2-DME, room temperature, 19 h; (2) NMP, 120°C, 17 h, 88%.



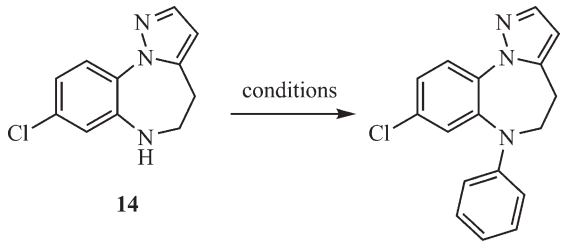

**5** **14**

(d, $J$ = 9.0 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 140.1, 135.5, 133.7, 125.0, 123.2, 117.4; HRMS (TOF, ES$^+$) $m/z$ [M + H]$^+$ calcd for $C_6H_7ClN_3O_2$: 188.0227; found: 188.0219.

**5-(2-(Benzyloxy)ethyl)-1-(4-chloro-2-nitrophenyl)-*1H*-pyrazole (13a).** A solution of 5-(benzyloxy)-1-(methoxy(methyl)amino)pent-1-en-3-one (23.5 g, 94.3 mmol) in methanol (380 mL) at 0°C was treated with (4-chloro-2-nitrophenyl)hydrazine hydrochloride (25.3 g, 113 mmol) and the reaction was warmed to reflux, treated with sodium carbonate (19.0 g, 179 mmol) in water (50 mL) over a 10-min period, and then stirred at reflux for 1.5 h. After this time, the reaction was cooled to ambient temperature and the volatiles were removed under reduced pressure. The resulting solution was diluted with ethyl acetate (750 mL), washed with water (700 mL) then brine (700 mL), dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The solid obtained was triturated with 1:9 ethyl acetate/heptane to afford 5-(2-(benzyloxy)ethyl)-1-(4-chloro-2-nitrophenyl)-*1H*-pyrazole (24.3 g, 72%) as light brown solid. The filtrate was concentrated under reduced pressure and the residue obtained was purified by chromatography (silica, heptane to 1:5 ethyl acetate/heptane) to afford additional 5-(2-(benzyloxy)ethyl)-1-(4-chloro-2-nitrophenyl)-*1H*-pyrazole (1.94 g, 6%) as red solid: mp 83–85°C; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, $J$ = 2.5 Hz, 1H), 7.61 (d, $J$ = 1.5 Hz, 1H), 7.58 (dd, $J$ = 8.5, 2.5 Hz, 1H), 7.44 (d, $J$ = 8.5 Hz, 1H), 7.35–7.28 (m, 3H), 7.24–7.22 (m, 2H), 6.30 (d, $J$ = 1.5 Hz, 1H), 4.45 (s, 2H), 3.67 (t, $J$ = 6.5 Hz, 2H), 2.85 (t, $J$ = 6.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 146.7, 142.3, 141.7, 137.8, 135.4, 133.1, 131.6, 130.9, 128.4, 127.8, 127.7, 125.4, 106.3, 73.2, 68.7, 26.5; HRMS (TOF, ES$^+$) $m/z$ [M + H]$^+$ calcd for $C_{18}H_{17}ClN_3O_3$: 358.0958; found: 358.0951.

**2-(1-(2-Amino-4-chlorophenyl)-1*H*-pyrazol-5-yl)ethanol (5).** A mixture of 5-(2-(benzyloxy)ethyl)-1-(4-chloro-2-nitrophenyl)-1*H*-pyrazole (2.98 g, 8.33 mmol) and 20% palladium hydroxide on carbon (614 mg, 50% water by weight) in THF (73 mL) was sparged with hydrogen for 5 min then stirred under an atmosphere of hydrogen (balloon) at ambient temperature for 16 h. After this time, the reaction was filtered through diatomaceous earth and the filtrate was concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, methylene chloride to ethyl acetate) to afford 2-(1-(2-amino-4-chlorophenyl)-1*H*-pyrazol-5-yl)ethanol (1.44 g, 73%) as white solid: mp 113–115°C; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 7.60 (d, $J$ = 2.0 Hz, 1H), 7.05 (d, $J$ = 8.5 Hz, 1H), 6.89 (d, $J$ = 2.0 Hz, 1H), 6.64 (dd, $J$ = 8.5, 2.5 Hz, 1H), 6.31 (d, $J$ = 2.0 Hz, 1H), 5.12 (s, 2H), 4.69 (t, $J$ = 5.5 Hz, 1H), 3.54–3.51 (m, 2H), 2.59 (t, $J$ = 7.0 Hz, 2H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 146.1, 141.5, 139.9, 133.6, 129.4, 122.8, 155.2, 114.7, 104.9, 59.5, 28.9; HRMS (TOF, ES$^+$) $m/z$ [M + H]$^+$ calcd for $C_{11}H_{13}ClN_3O$: 238.0747; found: 238.0741.

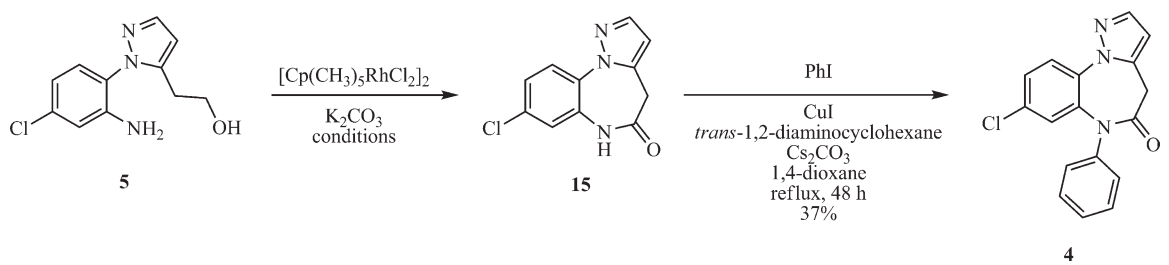
**Scheme 5.** Conditions: (a) *o*-$TMSC_6H_4OTf$, CsF, $CH_3CN$, room temperature, 3 days, 60%; (b) $PhB(OH)_2$, $Cu(OAc)_2$, $Et_3N$, 3 Å sieves, $CH_2Cl_2$, room temperature, 2.5 days, trace; (c) PhI, $Pd_2(dba)_3$, DavePhos, *t*-BuONa, toluene, 100°C, 4 h, 26%; (d) PhBr, $Pd(OAc)_2$, BINAP, *t*-BuOK, toluene, 100°C, 16 h, 23%; (e) PhBr, $Pd_2(dba)_3$, DavePhos, *t*-BuONa, toluene, 100°C, 4 h, 52%; (f) PhBr, $Pd_2(dba)_3$, JohnPhos, *t*-BuONa, toluene, 80°C, 16 h, 54%.




**14** **3**

**Preparation of 8-chloro-5,6-dihydro-4*H*-benzo[*b*]pyrazolo[1,5-*d*][1,4]diazepine (14).** A mixture of thionyl chloride (751 mg, 6.31 mmol) in 1,2-dimethoxyethane (32 mL) was treated with 2-(1-(2-amino-4-chlorophenyl)-1*H*-pyrazol-5-yl)ethanol (500 mg, 2.10 mmol) in 1,2-dimethoxyethane (10 mL) dropwise over 1 h at ambient temperature then the reaction was stirred at ambient temperature for 18 h. After this time, the reaction was treated dropwise with 2*M* aqueous sodium hydroxide over 20 min (pH ∼ 9) then the reaction was stirred at ambient temperature for 40 min. The reaction was extracted with ethyl acetate (150 mL then 75 mL) and the combined extracts were dried over sodium sulfate, filtered and the filtrate

**Scheme 6.** Conditions: (a) acetone, sealed tube, 100°C, 20 h, 14% yield, SM recovered; (b) acetone, sealed tube, 100°C, 45 h, 32% yield, SM recovered; (c) acetone, sealed tube, 120°C, 15 h, 42% yield, SM recovered; (d) acetone, sealed tube, 140°C, 7.5 h, 45% yield, SM recovered.




**5** **15** **4**

was concentrated under reduced pressure to afford 5-chloro-2-(5-(2-chloroethyl)-1*H*-pyrazol-1-yl)aniline (550 mg, quant., 98% pure by mass) as yellow oil which was used without further purification: $^1$H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, $J$ = 2.0 Hz, 1H), 7.02 (d, $J$ = 8.5 Hz, 1H), 6.84 (d, $J$ = 2.0 Hz, 1H), 6.78 (dd, $J$ = 8.0, 2.0 Hz, 1H), 6.35 (d, $J$ = 1.5 Hz, 1H), 3.90 (br s, 2H), 3.62 (t, $J$ = 7.0 Hz, 2H), 3.01 (t, $J$ = 7.5 Hz, 2H); HRMS (TOF, ES$^+$) $m/z$ $[M + H]^+$ calcd for $C_{11}H_{12}Cl_2N_3$: 256.0408; found: 256.0402.

A solution of 5-chloro-2-(5-(2-chloroethyl)-1*H*-pyrazol-1-yl)aniline (550 mg, 2.10 mmol, 98% pure by mass) in 1-methyl-2-pyrrolidinone (70 mL) was stirred at 120°C for 17 h. After this time, the reaction was cooled to ambient temperature, diluted with water (400 mL) and extracted with ethyl acetate (400 mL). The organic layer was washed with water (2 × 400 mL), 5% aqueous lithium chloride (3 × 400 mL) then brine (400 mL), dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, methylene chloride to 1:9 ethyl acetate/methylene chloride) to afford 8-chloro-5,6-dihydro-4*H*-benzo[*b*]pyrazolo[1,5-*d*][1,4]diazepine (407 mg, 88%) as off-white solid: mp 94–96°C; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, $J$ = 8.5 Hz, 1H), 7.58 (d, $J$ = 1.5 Hz, 1H), 6.89 (dd, $J$ = 8.5, 2.0 Hz, 1H), 6.77 (d, $J$ = 2.0 Hz, 1H), 6.18 (d, $J$ = 1.5 Hz, 1H), 3.91 (br s, 1H), 3.68–3.65 (m, 2H), 3.01 (t, $J$ = 5.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 142.1, 140.3, 138.8, 132.3, 125.6, 120.1, 119.4, 105.1, 48.7, 25.3; HRMS (TOF, ES$^+$) $m/z$ $[M + H]^+$ calcd for $C_{11}H_{11}ClN_3$: 220.0642; found: 220.0648.

**8-Chloro-6-phenyl-5,6-dihydro-4*H*-benzo[*b*]pyrazolo[1,5-*d*][1,4]diazepine (3).** A mixture of 8-chloro-5,6-dihydro-4*H*-benzo[*b*]pyrazolo[1,5-*d*][1,4]diazepine (120 mg, 0.546 mmol), tris(dibenzylideneacetone)dipalladium(0) (8 mg, 0.009 mmol), 2-(di-*tert*-butylphosphino)biphenyl (7 mg, 0.022 mmol), sodium *tert*-butoxide (61 mg, 0.637 mmol), and bromobenzene (71 mg, 0.455 mmol) in toluene (1.5 mL) was stirred at 80°C for 16 h. After this time, the reaction was cooled to ambient temperature, diluted with ethyl acetate (50 mL), and filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure and the residue obtained was purified by chromatography (silica, heptane to 2:3 ethyl acetate/heptane) to afford 8-chloro-6-phenyl-5,6-dihydro-4*H*-benzo[*b*]pyrazolo[1,5-*d*][1,4]diazepine (73 mg, 54%) as clear colorless film: $^1$H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, $J$ = 8.5 Hz, 1H), 7.60 (d, $J$ = 2.0 Hz, 1H), 7.29–7.26 (m, 2H), 7.20–7.16 (m, 2H), 6.87–6.84 (m, 1H), 6.77 (dd, $J$ = 8.5, 1.0 Hz, 2H), 6.23 (d, $J$ = 1.5 Hz, 1H), 3.97 (t, $J$ = 6.5 Hz, 2H), 3.00 (t, $J$ = 6.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 148.7, 140.9, 140.6, 139.6, 135.8, 133.0, 128.9, 128.9, 126.2, 125.4, 120.4, 117.4, 104.9, 53.9, 23.8; HRMS (TOF, ES$^+$) $m/z$ $[M + H]^+$ calcd for $C_{17}H_{15}ClN_3$: 296.0955; found: 296.0947.

**8-Chloro-4*H*-benzo[*b*]pyrazolo[1,5-*d*][1,4]diazepin-5(6*H*)-one (15).** A mixture of 5-(2-(benzyloxy)ethyl)-1-(4-chloro-2-nitrophenyl)-1*H*-pyrazole (119 mg, 0.500 mmol), potassium carbonate (7 mg, 0.050 mmol), and dichloro(pentamethylcyclopentadienyl)rhodium(III) dimer (8 mg, 0.013 mmol) in acetone (12.5 mL) was sparged with nitrogen for 10 min then it was stirred at 140°C in a heavy walled pressure vessel for 7.5 h. After this time, the reaction was cooled to ambient temperature and concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, heptane to 1:1 ethyl acetate/heptane) to afford 8-chloro-4*H*-benzo[*b*]pyrazolo[1,5-*d*][1,4]diazepin-5(6*H*)-one (53 mg, 45%) as off-white solid: mp >250°C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 10.36 (s, 1H), 7.83–7.79 (m, 2H), 7.38 (dd, $J$ = 9.0, 2.4 Hz, 1H), 7.31 (d, $J$ = 2.4 Hz, 1H), 6.43 (d, $J$ = 1.5 Hz, 1H), 3.70 (s, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 169.1, 142.3, 137.2, 131.2, 130.7, 129.7, 125.1, 124.8, 121.8, 105.5, 32.9; HRMS (TOF, ES$^+$) $m/z$ $[M + H]^+$ calcd for $C_{11}H_9ClN_3O$: 234.0434; found: 234.0439.

**8-Chloro-6-phenyl-4*H*-benzo[*b*]pyrazolo[1,5-*d*][1,4]diazepin-5(6*H*)-one (4).** A mixture of 8-chloro-4*H*-benzo[*b*]pyrazolo[1,5-*d*][1,4]diazepin-5(6*H*)-one (51 mg, 0.218 mmol), cesium carbonate (213 mg, 0.654 mmol), and copper(I) iodide (8 mg, 0.044 mmol) in 1,4-dioxane (1.5 mL) was treated with iodobenzene (133 mg, 0.654 mmol) and *trans*-cyclohexane-1,2-diamine (5 mg, 0.044 mmol) and the resulting mixture was sparged with argon for 2 min then stirred at 102°C for 48 h. After this time, the reaction was cooled to ambient temperature, diluted with methylene chloride (10 mL), filtered through diatomaceous earth, rinsed with 1:9 methanol/methylene chloride (50 mL), and the filtrate was concentrated under reduced pressure. The residue obtained was purified by chromatography (silica, methylene chloride to 1:9 ethyl acetate/methylene chloride), solvent exchanged with acetonitrile, and freeze dried from acetonitrile/water to afford 8-chloro-6-phenyl-4*H*-benzo[*b*]pyrazolo[1,5-*d*][1,4]diazepin-5(6*H*)-one (25 mg, 37%) as off-white solid: mp 83–84°C; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 7.88–7.83 (m, 2H), 7.49–7.34 (m, 4H), 7.17–7.15 (m, 2H), 6.94 (d, $J$ = 2.5 Hz, 1H), 6.51 (d, $J$ = 1.5 Hz, 1H), 3.92–3.81 (m, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 167.2, 142.7, 141.4, 138.2, 134.8, 131.5, 131.1, 129.4, 128.3, 127.6, 126.5, 125.8, 125.5, 105.5, 33.3; HRMS (TOF, ES$^+$) $m/z$ $[M + H]^+$ calcd for $C_{17}H_{13}ClN_3O$: 310.0747; found: 310.0745.

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