JOC The Journal of Organic Chemistry

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The Formation of Seven-Membered Heterocycles under Mild Pictet–Spengler Conditions: A Route to Pyrazolo[3,4]benzodiazepines

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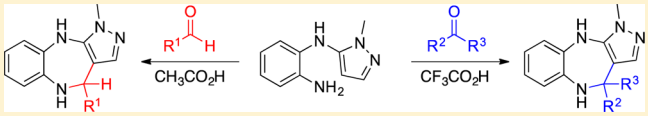
Supporting Information

ABSTRACT: Reported is a method for the synthesis of seven-membered heterocycles via a Pictet–Spengler condensation reaction under very mild conditions. High substrate scope allows for use of aldehydes using catalytic amounts of acetic acid yielding 39–90% and ketones using catalytic amounts of trifluoroacetic acid yielding 25–83%.



The Pictet–Spengler reaction was originally reported in 1911[1] and has found prominence for the synthesis of many functional molecules. Some important examples include tetrahydroisoquinolines (THIQs) and tetrahydro-β-carbolines (THBCs) comprising the backbones of important pharmaceuticals such as nomifensine and potential anti-alzheimer's medication.[2] Recent developments have allowed the Pictet–Spengler cyclization to be applied to the synthesis of anticancer molecules[3] and antitubecular-type compounds.[4]

Pictet–Spengler reactions are often utilized in the synthesis of six-membered rings, and the conditions for the carbon–carbon bond formation can vary from quite mild to much more trying conditions. Some report the use of acetic acid (AcOH)[5] or trifluoroacetic acid (TFA)[6] as the acid catalyst and typically in a solvent brought to reflux.[7] There are also examples of more unfavorable reactions, such as using superacids to promote the reaction.[8] In contrast, there have only been a few reports on the synthesis of seven-membered rings via a Pictet–Spengler reaction pathway, and these have required a combination of strong acids and/or high temperatures to promote the reaction.[8b,9b–e] Reported within is a synthetic strategy for the synthesis of seven-membered heterocycles in moderate to high yields using very mild conditions in comparison to previously reported methods

Seven-membered heterocycles are an important class of molecules because of their biological utility[10] and have been an area of focus for our group.[11] Our current research is to develop syntheses of biologically important heterocycles, and as such, we were interested in developing a simple procedure for the synthesis of benzodiazepines with substitution at the 8-position (Figure 1).

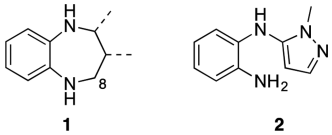
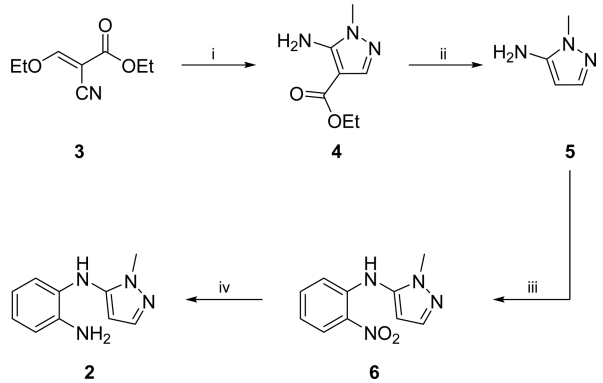


Figure 1. Targeted class of benzodiazepine **1** and targeted test substrate **2**.

The initial approach was to develop conditions that allowed for the mild cyclization of compound **2** using the Pictet–Spengler reaction. The motivation for using compound **2** as the test substrate was 3-fold: (1) it afforded useful compounds for our research into oxytocin and vasopressin antagonism;[12] (2) the aniline aromaticity aids the formation of the more electrophilic iminium ion;[7] and (3) the electron-rich pyrazole should favor cyclization, with a related moiety already employed in a Pictet–Spengler reaction,[9e] making it the ideal substrate.

The synthetic pathway to obtain compound **2** is shown in Scheme 1. Cyclocondensation of methyl hydrazine with substituted acrylate **3** afforded the amino-ester pyrazole **4**,[13] which, following saponification and heat promoted decarboxylation, affords aminopyrazole **5**.[14] Electrophilic aromatic

Scheme 1. Synthesis of Pictet–Spengler Starting Material 2[a]



[a]Reagents and conditions: (i) $MeNHNH_2$, EtOH, reflux, 2 h, 85%; (ii) (a) NaOH (3 M), MeOH, reflux, 3 h; (b) 185 °C; 87% over 2 steps; (iii) KO^{t}Bu, *o*-fluoronitrobenzene, THF, 0 °C–RT, 1 h, 75%; (iv) Pd/C, H_2, EtOAc, RT, 36 h, 99%.

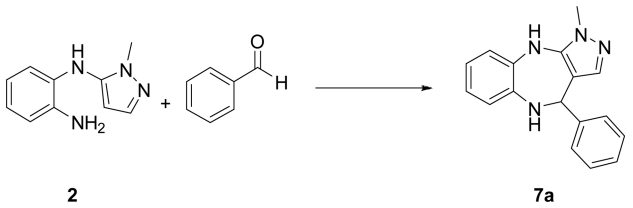
Received: April 2, 2016
Published: May 9, 2016

DOI: 10.1021/acs.joc.6b00710
J. Org. Chem. 2016, 81, 4883–4889

substitution with *o*-fluoronitrobenzene leads to compound **6**, which is then reduced to form the requisite aniline **2**.

With compound **2** in hand, we could then investigate its ability to undergo a Pictet–Spengler reaction. Benzaldehyde was chosen as the aldehyde to optimize reaction conditions, and we were gratified to see with the addition of TFA the formation of benzodiazepine **7a** (Scheme 2, entry 1).

Scheme 2. Pictet–Spengler Cyclization Reaction[a]



2 **7a**

[a]See Table 1 for conditions.

With the success of the reaction we investigated the influence of solvent and catalyst for this reaction (Table 1). Initially we tested the necessity of the acid for this reaction (entry 2), which resulted in no reaction. Using TFA in dichloromethane the reaction proceeded rapidly (under 10 min), so in order to better understand the influence of the acid, a stronger and weaker acid were trialed. 50 mol % of hydrochloric acid (3 M in water) and acetic acid were tested (entries 3 and 4), but little difference was observed for both yield and reaction rate so we then explored the catalyst loading as a factor. Using acetic acid due to its low cost and high availability, we decreased catalyst loading (entry 5) and found that only using 20 mol % of acetic acid allows for slightly better yields but a decrease in the reaction rate of up to approximately 2 h. With the optimized catalyst loading established, we then attempted optimization of the reaction using various solvents. Dichloromethane and acetonitrile showed the highest yields (entries 5 and 6), although the reaction was faster in acetonitrile (1 h vs 2 h). The reaction still progressed with comparable yields using toluene, tetrahydrofuran, and ethanol (entries 6–9). All solvents were used as bottle reagents without drying, which suggested trace amounts of water could be tolerated. Furthermore, entry 3 showed that water in greater than trace amounts was well tolerated, and hence in order to evaluate the other extreme, we attempted a reaction using water as the solvent (entry 10). No obvious dissolution of the aniline was observed, however the reaction still afforded **7a** in 74% yield, suggesting an "on water" reaction. One would expect water to disfavor the reaction by shifting the equilibrium in favor of the aldehyde and aniline rather than the requisite imine. This result suggests that the reactivity of this system is such that the rate-limiting step is imine formation and that once formed, cyclization occurs quickly. With optimized conditions of using 20 mol % of acetic acid in acetonitrile (entry 6), we could then explore the range of aldehydes this reaction could accommodate (Table 2).

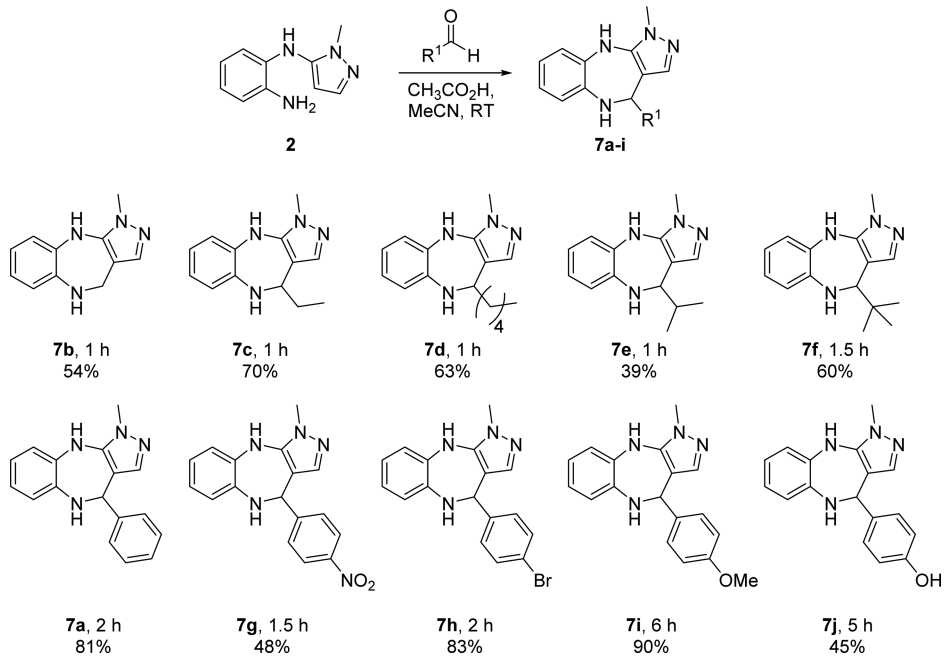
Table 1. Acid and Solvent Screen[a]

entry	acid	mol %	solvent	yield (%)
1	TFA	50	CH_2Cl_2	70
2	–	–	CH_2Cl_2	NR
3	HCl[b]	50	CH_2Cl_2	74
4	AcOH	50	CH_2Cl_2	73
5	AcOH	20	CH_2Cl_2	75
6	AcOH	20	MeCN	76
7	AcOH	20	PhMe	68
8	AcOH	20	THF	65
9	AcOH	20	EtOH	70
10	AcOH	20	H_2O	74

[a]All reactions were conducted at room temperature. [b]3 M HCl in water.

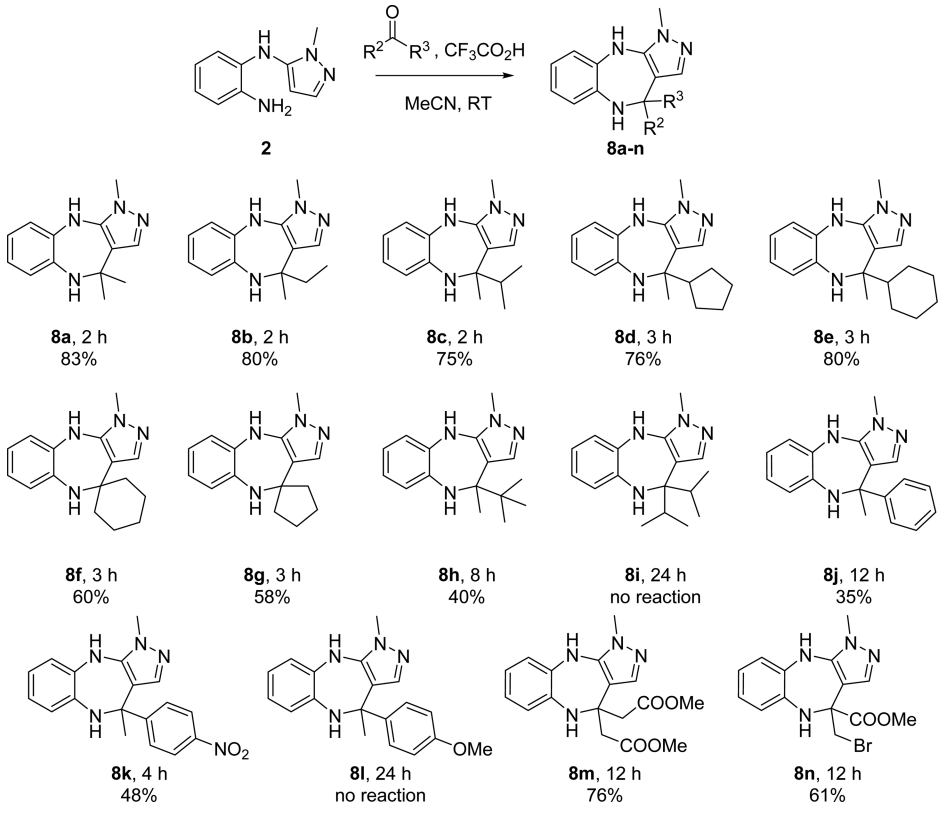
Initially we tested the simplest aldehyde, formaldehyde, which afforded unsubstituted benzodiazepine **7b**. Knowing that water could be tolerated in this reaction, we were able to use formaldehyde as a 37% aqueous solution. The synthesis of **7b**

Table 2. Substrate Scope of Aliphatic and Aromatic Aldehydes



DOI: 10.1021/acs.joc.6b00710
J. Org. Chem. 2016, 81, 4883–4889

Table 3. Scope of Ketones Using TFA in Acetonitrile



has been previously reported via intramolecular lactamization followed by subsequent reduction[7] or reductive amination.[15] Previously unreported benzodiazepines **7c** and **7d** could also be synthesized and demonstrated that longer aliphatic aldehydes propanal and hexanal are well tolerated. The effect of steric bulk of the aldehyde was also investigated using isobutyraldehyde and pivalaldehyde both of which afforded target compounds **7e** and **7f**, respectively, without a significant difference in yield or reaction time.

We then looked toward substituted benzaldehydes to explore the electronic limitations that may be present for this transformation. We have already shown that benzaldehyde was an acceptable electrophile to afford **7a**. The incorporation of an electron-withdrawing group was anticipated to activate the aldehyde evidenced by the condensation of *p*-nitrobenzaldehyde. The dramatic increase in the rate of formation of product **7g** is suggestive of increased electrophilicity, however the decreased yield indicates increased reactivity of this aldehyde has led to unwanted side reactions. When *p*-bromobenzaldehyde was employed, then **7h** was obtained in an improved 83% yield, suggesting optimal electronics. Compound **7h** has the added benefit of the halogen acting as a handle for further reactions by cross coupling. To further investigate the influence of electronics on the reaction, we then focused on electron-rich aldehydes first using *p*-methoxybenzaldehyde to yield compound **7i**. A longer reaction time of 6 h was required to reach completion, illustrating the reduced reactivity of the aldehyde due to electronic effects. Surprisingly though, an increased yield of 90% was obtained. Finally, the use of *p*-hydroxybenzaldehyde showed that a free OH combined with electron donation was tolerated in the reaction to afford compound **7j**.

With the success of the aldehydes, we predicted that equal success could be achieved when employing ketones in the Pictet–Spengler reaction (Table 3). A similar approach was taken when determining the substrate scope, starting with the simplest ketone, acetone, which afforded compound **8a**. Using acetic acid for this transformation resulted in low yields and long reaction times (32% after 6 h). It was found that a stronger acid, in this case TFA, was required to affect the desired transformation and that the reaction was slightly slower than with aliphatic aldehydes (2 h vs 1 h). However, the acid was still only required in catalytic quantities, and the reaction progressed at room temperature. Reaction with butanone yielded benzodiazepine **8b** in equally good yield. In an attempt to increase steric bulk, isopropyl methyl ketone was used with TFA to form **8c**. In this instance the reaction did not proceed when using acetic acid after 24 h at room temperature. This same reaction mixture was heated, and the desired product was not formed. From this point on we only used TFA for investigating the scope of the reaction with ketones.

Attempting to increase the steric bulk further, cyclopentyl methyl ketone and cyclohexyl methyl ketone yielded compounds **8d** and **8e**, respectively. Formation of spirocyclic benzodiazepines **8f** and **8g** was achieved using cyclopentanone and cyclohexanone, respectively, although in slightly lower yields. It was realized that the steric properties of the substrates were impacting on the reaction yields, as pinacolone (3,3-dimethyl-2-butanone) only produced compound **8h** in 40% yield. The steric limitation was found when diisopropyl ketone was attempted, and after 24 h only starting material was recovered.

To test the aromatic ketones, *p*-nitroacetophenone was initially used and afforded benzodiazepine **8k** in moderate yield. Acetophenone afforded compound **8j** with a reduction in yield,

DOI: 10.1021/acs.joc.6b00710
J. Org. Chem. 2016, 81, 4883–4889

showing that the earlier presence of the electron-withdrawing effect of the nitro group was significant. Finally, using *p*-methoxyacetophenone proved far too electronically unfavorable for progression, as no reaction was observed after 24 h even with heating to reflux.

The use of more functionally diverse ketones was illustrated with the use of 3-oxopentanedioate as a substrate to afford **8m**. Further functionalizing this substrate to establish enhanced tolerability, we tested the reaction with methyl 3-bromo-2-oxopropanoate affording the appropriately cyclized product **8n**. This successful result illustrates that even with three electrophilic sites in the substrate, the carbon bearing the bromine, the ketone, and the ester, the imine formation and cyclization was still the most favorable reaction pathway.

In summary, we have described very mild Pictet–Spengler conditions for the formation of seven-membered heterocycles. This approach allows for the ease of formation of privileged scaffolds with extremely mild conditions and a high substrate scope that is compatible with various solvents and acids. The benzodiazepines reported herein contain important functionality to be included in our research toward compounds active in the central nervous system.

EXPERIMENTAL SECTION

Unless noted otherwise, commercially obtained reagents were used as purchased without further purification. Solvents for flash chromatography were distilled prior to use or used as purchased for HPLC grade, with the eluent mixture reported as the volume/volume ratio (v/v). Melting points were measured with a ramp rate of 0.5–2.0 °C/min and are uncorrected. Infrared absorption spectra were reported as vibrational frequency (cm^{-1}). Nuclear magnetic resonance spectra were recorded at 298 K unless stated otherwise, using either a 300 or a 500 MHz spectrometer. The data are reported as the chemical shift (Δ, ppm) relative to the solvent residual peak, relative integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad, dd = doublet of doublets, etc.), coupling constant (*J*, Hz). Low-resolution mass spectra (LRMS) were recorded using electrospray ionization (ESI). High-resolution mass spectra were run recorded using a Fourier transform ion cyclotron resonance mass spectrometer.

1-Methyl-1*H*-pyrazol-5-amine (5). Compound **4**[13] (20.0 g, 118 mmol) in ethanol (100 mL) was treated with aqueous sodium hydroxide (50 mL, 3 M). The reaction mixture was heated to reflux and allowed to stir for 2 h, and the ethanol removed under reduced pressure. The aqueous solution was cooled to 0 °C and acidified to pH 5. The white precipitate was collected by filtration and heated neat to 185 °C, and the sublimed material collected with a coldfinger trap to afford compound **4** (10.0 g, 87%) as a light brown solid. MP 73–74 °C; IR (Diamond Cell, neat) 3395, 3134, 1643, 1556, 1517, 1431, 1344, 1268, 1207, 999, 928, 758, 632 cm^{-1}. ^1H NMR (300 MHz, chloroform-*d*) δ 7.21 (d, *J* = 2.0 Hz, 1H), 5.49 (d, *J* = 2.0 Hz, 1H), 3.62 (s, 3H), 3.50 (br. s, 2H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 144.6 (C), 138.2 (CH), 91.2 (CH), 34.3 (CH_3). LRMS (ESI+) *m*/*z*: 98 (100, $[M + H]^+$), 120 (50, $[M + Na]^+$). These data matched that previously reported.[14]

1-Methyl-*N*-(2-nitrophenyl)-1*H*-pyrazol-5-amine (6). To a magnetically stirred solution of amine **5** (10 g, 103 mmol) in dry THF (300 mL), potassium *tert*-butoxide (23 g, 205 mmol) was added at 0 °C and allowed to stir for 30 min. The resultant suspension was treated with *o*-fluoronitrobenzene (12 mL, 113 mmol) at 0 °C. Reaction was brought to room temperature and allowed to stir for 1 h. Reaction was quenched with water (300 mL) and extracted with ethyl acetate (3 × 200 mL). Organic extracts were dried ($MgSO_4$), and solvent removed under reduced pressure. The bright yellow residue was taken up in dichloromethane and purified by flash column chromatography (silica, 3:5 ethyl acetate/hexane) to afford compound **6** (16.4 g, 75%) as a yellow solid. MP: 133–135 °C; IR (Diamond cell, neat): 3297, 3094, 1609, 1572, 1509, 1490, 1340, 1221, 1145, 1075, 1043, 927, 750 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 9.11 (s, 1H), 8.25 (d, *J* = 10.1 Hz, 1H), 7.56 (s, 1H), 7.52–7.38 (m, 1H), 6.96–6.84 (m, 1H), 6.78 (s, 1H), 6.20 (d, *J* = 2.5 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 142.7 (C), 139.0 (CH), 136.8 (C), 136.3 (C), 133.4 (CH), 126.6 (CH), 118.7 (CH), 115.8 (CH), 101.8 (CH), 35.2 (CH_3); LRMS (+ESI): *m*/*z* 219 (100, $[M + H]^+$); HRMS (+ESI): $[M + Na]^+$ calcd for $C_{10}H_{10}NaN_4O_2$: 241.0696; found 241.0697

***N*^{1}-(1-Methyl-1*H*-pyrazol-5-yl)benzene-1,2-diamine (2).** Compound **6** (16.4 g, 75.1 mmol) and 10% (w/w) palladium on carbon (800 mg) in ethyl acetate (250 mL) was stirred under a hydrogen atmosphere for 36 h. The mixture was filtered through basic alumina and Celite washing with ethyl acetate, and the filtrate concentrated under reduced pressure to afford compound **2** (14.06 g, 99%) as a light pink crystalline solid. MP: 134–135 °C; IR (Diamond cell, neat): 3326, 3213, 1554, 1498, 1430, 1384, 1281, 993, 927, 733, 627 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 7.40 (d, *J* = 1.9 Hz, 1H), 6.92–6.82 (m, 1H), 6.83–6.70 (m, 2H), 6.63 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.81 (d, *J* = 1.9 Hz, 1H), 5.26 (s, 1H), 3.64 (s, 3H), 3.49 (br. s, 2H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 142.1 (C), 138.5 (CH), 136.6 (C), 132.2 (C), 122.9 (CH), 120.3 (CH), 117.9 (CH), 117.3 (CH), 96.7 (CH), 34.9 (CH_3); LRMS (+ESI) *m*/*z*: 189 (100, $[M + H]^+$), 211 (80, $[M + Na]^+$); HRMS (+ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{10}H_{12}NaN_4$: 211.0954; found 211.0955.

General Procedure A for the Pictet–Spengler Reaction with Aldehydes. Compound **2** (100 mg, 0.56 mmol) and appropriate aldehyde (0.62 mmol) in acetonitrile (5 mL) was treated with acetic acid (65 μL, 20 mol %) and allowed to stir at room temperature. Reaction progress was monitored by TLC and upon completion was concentrated under reduced pressure, taken up in $NaHCO_3$, and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil was subjected to column chromatography (silica, ethyl acetate/hexane, 3:2 (v/v)) to afford compounds **7a–i**.

*1-Methyl-4-phenyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine (**7a**).* Compound **2** was subjected to General Procedure A with benzaldehyde (0.063 mL, 0.62 mmoL) and then recrystallized with dichloromethane/hexane to afford **7a** (118 mg, 81%) as a yellow crystalline solid. MP: 125–126 °C; IR (Diamond cell, neat): 3263, 2333, 2215, 1649, 1563, 1493, 1432, 1291, 993, 748, 701 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 7.43–7.29 (m, 5H), 6.99–6.78 (m, 3H), 6.77–6.68 (m, 1H), 6.65 (s, 1H), 5.95 (br. s, 1H), 5.18 (s, 1H), 3.77 (s, 3H), 1 NH not observed; ^{13}C NMR (75 MHz, chloroform-*d*) δ 142.7 (C), 140.0 (C), 137.4 (C), 137.0 (CH), 133.6 (C), 128.7 (2 CH), 128.1 (CH), 128.0 (2 CH), 123.5 (CH), 123.0 (CH), 122.2 (CH), 119.0 (CH), 105.9 (C), 59.8 (CH), 34.7 (CH_3); LRMS (+ESI) *m*/*z*: 277 (100, $[M + H]^+$); HRMS (+ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{17}N_4$: 277.1448; found 277.1446.

*1-Methyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine (**7b**).* Compound **2** was subjected to General Procedure A with formaldehyde (24 μL of a 37% aqueous solution, 0.62 mmoL) to afford **7b** (57 mg, 54%) as an off-white solid. MP: 205–207 °C; IR (Diamond cell, neat): 3386, 3362, 3251, 3150, 3046, 2788, 1604, 1570, 1315, 991, 819, 754, 627 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 7.12 (s, 1H), 6.96–6.76 (m, 4H), 5.81 (br. s, 1H), 4.10 (s, 2H), 3.73 (s, 3H), 1.70 (br. s, 1H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 140.4 (C), 138.8 (C), 135.9 (CH), 133.4 (C), 123.0 (CH), 122.8 (CH), 122.2 (CH), 119.1 (CH), 101.9 (C), 44.7 (CH_2), 34.6 (CH_3); LRMS (+ESI) *m*/*z*: 201 (100, $[M + H]^+$), 223 (40, $[M + Na]^+$); HRMS (+ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{11}H_{12}NaN_4$: 223.0954; found 223.0958.

*4-Ethyl-1-methyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine (**7c**).* Compound **2** was subjected to General Procedure A with propanal (45 μL, 0.62 mmoL) to afford **7c** (85 mg, 70%) as an off-white solid. MP: 163–164 °C; IR (Diamond cell, neat): 3369. 3254, 3048, 2965, 2922, 1604, 1572, 1432, 1389, 1313, 1292, 1178, 1160, 1106, 988, 754, 693, 626 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 7.13 (s, 1H), 6.93–6.74 (m, 4H), 6.02 (br. s, 1H), 4.14–3.94 (m, 1H), 3.93 (br. s, 1H), 3.71 (s, 3H), 1.81–1.57 (m, 2H),

DOI: 10.1021/acs.joc.6b00710
J. Org. Chem. 2016, 81, 4883–4889

1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 139.8 (C), 136.4 (C), 135.9 (CH), 133.9 (C), 123.7 (CH), 122.7 (CH), 122.0 (CH), 118.8 (CH), 105.8 (C), 55.9 (C), 34.6 (CH_3), 30.7 (CH_2), 10.6 (CH_3); LRMS (+ESI) m/z: 229 (100, $[M + H]^+$); HRMS (+ESI) m/z: $[M + Na]^+$ calcd for $C_{13}H_{16}NaN_4$: 251.1267; found 251.1271.

*1-Methyl-4-pentyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine (**7d**).* Compound **2** was subjected to General Procedure A with hexanal (76 μL, 0.62 mmoL) to afford **7d** (90 mg, 63%) as a light brown oil. IR (Diamond cell, thin film): 3283, 3101, 2954, 2928, 1571,1501, 1434, 1298, 750 cm^{-1}; ^{1}H NMR (300 MHz, chloroform-d) δ 7.11 (s, 1H), 6.90−6.73 (m, 4H), 6.21 (br. s, 1H), 4.08 (t, J = 6.6 Hz, 1H), 3.68 (s, 3H), 3.51 (br. s, 1H), 1.65 (q, J = 7.4, 6.7 Hz, 2H), 1.54−1.19 (m, 6H), 0.96−0.78 (m, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 139.9 (C), 136.4 (C), 135.7 (CH), 133.8 (C), 123.6 (CH), 122.6 (CH), 121.9 (CH), 118.8 (CH), 106.0 (C), 54.5 (CH), 37.7 (CH_2), 34.6 (CH_3), 31.7 (CH_2), 25.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3); LRMS (+ESI) m/z: 271 (100, $[M + H]^+$); HRMS (+ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{22}NaN_4$: 293.1737; found 293.1737.

*4-Isopropyl-1-methyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine (**7e**).* Compound **2** was subjected to General Procedure A with isobutyraldehyde (57 μL, 0.62 mmoL) to afford **7e** (50 mg, 39%) as a white solid. MP: 156−157 °C; IR (Diamond cell, neat): 3278, 2955, 1563, 1498, 1432, 1382, 1295, 1261, 993, 926, 854, 743 cm^{-1}; ^{1}H NMR (300 MHz, chloroform-d) δ 7.09 (s, 1H), 6.89−6.69 (m, 4H), 6.17 (br. s, 1H), 3.74 (d, J = 7.7 Hz, 1H), 3.68 (s, 3H), 1.79 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1 NH not observed; ^{13}C NMR (75 MHz, chloroform-d) δ 139.9 (C), 136.9 (CH), 136.0 (C), 133.2 (C), 123.4 (CH), 122.2 (CH), 121.6 (CH), 118.5 (CH), 104.6 (C), 60.7 (CH), 34.6 (CH_3), 34.1 (CH), 20.4 (CH_3), 18.7 (CH_3); LRMS (+ESI) m/z: 243 (100, $[M + H]^+$); HRMS (+ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{19}N_4$: 243.1604; found 243.1604.

*4-(tert-Butyl)-1-methyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine (**7f**).* Compound **2** was subjected to General Procedure A with pivalaldehyde (65 μL, 0.62 mmoL) to afford **7f** (81 mg, 60%) as a light purple solid. MP: 181−182 °C; IR (Diamond cell, neat): 3383, 3288, 2960, 2864, 1571, 1497, 1432, 1386, 1359, 1314, 1090, 989, 883, 863, 775, 737, 708 cm^{-1}; ^{1}H NMR (300 MHz, chloroform-d) δ 7.10 (s, 1H), 6.83−6.64 (m, 4H), 5.98 (br. s, 1H), 3.83 (s, 1H), 3.72 (s, 3H), 0.88 (s, 9H), 1NH not observed; ^{13}C NMR (75 MHz, chloroform-d) δ 140.4 (C), 137.9 (CH), 136.3 (C), 131.3 (C), 122.1 (CH), 121.4 (CH), 121.1 (CH), 118.1 (CH), 102.4 (C), 63.3 (CH), 38.8 (C), 34.6 (CH_3), 27.2 (3 CH_3); LRMS (+ESI) m/z: 256 (100, $[M + H]^+$), 279 (40, $[M + Na]^+$); HRMS (+ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{21}N_4$: 257.1761; found 257.1766.

*1-Methyl-4-(4-nitrophenyl)-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine (**7g**).* Compound **2** was subjected to General Procedure A with p-nitrobenzaldehyde (94 mg, 0.62 mmoL) to afford **7g** (82 mg, 48%) as a red solid. MP: 174−175 °C; IR (Diamond cell, neat): 3399, 1594, 1558, 1505, 1343, 1321, 1283, 1108, 996, 932, 846, 755, 716, 685, 634 cm^{-1}; ^{1}H NMR (300 MHz, chloroform-d) δ 8.74 (s, 1H), 8.35 (d, J = 8.7 Hz, 2H), 8.09 (d, J = 8.7 Hz, 2H), 7.51 (s, 1H), 7.27−7.13 (m, 2H), 6.88 (td, J = 7.6, 1.3 Hz, 1H), 6.72 (dd, J = 8.2, 1.3 Hz, 1H), 6.67 (s, 1H), 6.13 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 154.8 (CH), 149.4 (C), 141.6 (C), 141.2 (C), 140.0 (C), 138.8, (CH) 135.5 (C), 129.6 (CH), 129.4 (2 CH), 124.3 (2 CH), 119.8 (CH), 116.8 (CH), 113.5 (CH), 99.7 (CH), 35.2 (CH_3); LRMS (+ESI) m/z: 322 (100, $[M + H]^+$), 279 (30, $[M + Na]^+$); HRMS (+ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}N_5O_2$: 322.1299; found 322.1298.

*4-(4-Bromophenyl)-1-methyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine (**7h**).* Compound **2** was subjected to General Procedure A with p-bromobenzaldehyde (114 mg, 0.62 mmoL) to afford **7h** (188 mg, 83%) as an off white-solid. MP: 165−166 °C; IR (Diamond cell, neat): 3326, 3028, 1571, 1499, 1485, 1437, 1310, 1291, 1069, 1007, 853, 811, 800, 748 cm^{-1}; ^{1}H NMR (300 MHz, chloroform-d) δ 7.47 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 6.97−6.77 (m, 3H), 6.73−6.63 (m, 2H), 5.96 (br. s, 1H), 5.15 (s, 1H), 3.77 (s, 3H), 1 NH not observed; ^{13}C NMR (75 MHz, chloroform-d) δ 141.9 (C), 139.9 (C), 137.0 (CH), 133.8 (C), 131.9 (2 CH), 129.7 (2 CH), 123.8 (CH), 123.4 (CH), 122.6 (CH), 122.0 (C), 119.1 (CH), 105.2 (C), 59.2 (CH), 34.7 (CH_3); LRMS (+ESI) m/z: 355/357 (100, $[M + H]^+$), 377/379 (20, $[M + Na]^+$); HRMS (+ESI) m/z: $[M + Na]^+$ calcd for $C_{17}H_{15}BrNaN_4$: 377.0372/379.0352; found 377.0372/379.0351.

*4-(4-Methoxyphenyl)-1-methyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine (**7i**).* Compound **2** was subjected to General Procedure A with p-methoxybenzaldehyde (75 μL, 0.62 mmoL) to afford **7i** (146 mg, 90%) as an off white-solid. MP: 159−160 °C; IR (Diamond cell, neat): 3267, 3199, 3153, 3050, 2952, 1604, 1570, 1507, 1437, 1307, 1243, 1171, 1022, 752, 640 cm^{-1}; ^{1}H NMR (300 MHz, chloroform-d) δ 7.29 (d, J = 8.6 Hz, 2H), 6.96−6.78 (m, 5H), 6.72 (d, J = 7.4 Hz, 1H), 6.65 (s, 1H), 5.91 (br. s, 1H), 5.11 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 1 NH not observed; ^{13}C NMR (75 MHz, chloroform-d) δ 159.5 (C), 139.8 (C), 137.6 (C), 137.2 (CH), 135.2 (C), 133.6 (C), 129.3 (2 CH), 123.6 (CH), 123.1 (CH), 122.4 (CH), 119.0 (CH), 114.1 (2 CH), 106.3 (C), 59.3 (CH), 55.4 (CH_3), 34.7 (CH_3); LRMS (+ESI) m/z: 307 (100, $[M + H]^+$), 329 (40, $[M + Na]^+$); HRMS (+ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{19}N_4O$: 307.1553; found 307.1552.

*4-(1-Methyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]-diazepin-4-yl)phenol (**7j**).* Compound **2** was subjected to General Procedure A with p-hydroxybenzaldehyde (76 mg, 0.62 mmol) to afford **7j** as an off white solid that was collected by filtration from the reaction. MP: 202−203 °C; IR (Diamond Cell, neat): 3608, 3275, 1565, 1495, 1436, 1385, 1291, 1249, 1188, 1001, 816, 744 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.43 (br s., 1H), 7.50 (s, 1H), 7.16 (d, J = 7.8 Hz, 2H), 7.03 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.81−6.71 (m, 2H), 6.68 (t, J = 7.5 Hz, 1H), 6.55 (s, 1H), 5.10 (s, 1H), 4.68 (br. s, 1H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 157.5 (C), 141.1 (C), 138.8 (C), 137.0 (CH), 136.0 (C), 135.0 (C), 129.8 (2 CH), 124.0 (CH), 122.5 (CH), 121.8 (CH), 119.6 (CH), 115.7 (2 CH), 106.6 (C), 59.4 (CH), 35.1 (CH_3); LRMS (+ESI) m/z: 293 (100, $[M + H]^+$), 315 (40, $[M + Na]^+$); HRMS (+ESI) m/z: $[M + Na]^+$ calcd for $C_{17}H_{16}NaN_4O$: 315.1216; found 315.1220.

General Procedure B for the Pictet−Spengler Reaction with Ketones. Compound **2** (100 mg, 0.56 mmol) and appropriate ketone (0.62 mmol) in acetonitrile (5 mL) was treated with trifluoroacetic acid (5 μL, 10 mol %) and allowed to stir at room temperature. Reaction progress was monitored by TLC and upon completion was concentrated, taken up in $NaHCO_3$, and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil subjected to column chromatography (ethyl acetate/hexane, 3:2) to afford compounds **8a−m**.

*1,4,4-Trimethyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]-diazepine (**8a**).* Compound **2** was subjected to General Procedure B with acetone (45 μL, 0.62 mmoL) to afford **8a** (100 mg, 83%) as an off-white crystalline solid. MP: 130−131 °C; IR (Diamond cell, neat): 3279, 2963, 1561, 1494, 1434, 1381, 1309, 1264, 1201, 1165, 991, 90, 853, 755, 733, 629 cm^{-1}; ^{1}H NMR (300 MHz, chloroform-d) δ 7.14 (s, 1H), 6.94−6.74 (m, 4H), 5.96 (br. s, 1H), 3.70 (s, 3H), 3.09 (br. s, 1H), 1.47 (s, 6H); ^{13}C NMR (75 MHz, chloroform-d) δ 138.8 (C), 135.9 (C), 135.0 (CH), 134.2 (C), 124.3 (CH), 122.9 (CH), 122.1 (CH), 118.6 (CH), 110.8 (C), 53.8 (C), 34.6 (CH_3), 32.3 (2CH_3); LRMS (+ESI) m/z: 229 (100, $[M + H]^+$); HRMS (+ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{17}N_4$: 229.1448; found 229.1447.

*4-Ethyl-1,4-dimethyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine (**8b**).* Compound **2** was subjected to General Procedure B with butan-2-one (55 μL, 0.62 mmoL) to afford **8b** (103 mg, 80%) as a clear crystalline solid. MP: 155−156 °C; IR (Diamond cell, neat): 3308, 3255, 2960, 1563, 1495, 1434, 1375, 1201, 996, 762, 669, 469 cm^{-1}; ^{1}H NMR (300 MHz, chloroform-d) δ 7.11 (s, 1H), 6.93−6.73 (m, 4H), 5.86 (br. s, 1H), 3.72 (s, 3H), 3.54 (br. s, 1H), 1.82−1.50 (m, 2H), 1.43 (s, 3H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 139.0 (C), 135.7 (CH), 135.6 (C), 133.8 (C), 124.2 (CH), 122.6 (CH), 122.0 (CH), 118.4 (CH), 109.5 (C), 56.6 (C), 37.2 (CH_2), 34.7 (CH_3), 28.8 (CH_3), 8.9 (CH_3);

DOI: 10.1021/acs.joc.6b00710
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LRMS (+ESI) *m/z*: 243 (100, $[M + H]^+$) 265 (20, $[M + Na]^+$); HRMS (+ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{19}N_4$: 243.1604; found 243.1604.

*4-Isopropyl-1,4-dimethyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo-[3,4-e][1,4]diazepine (**8c**).* Compound **2** was subjected to General Procedure B with 3-methylbutan-2-one (67 μL, 0.62 mmoL) to afford **8c** (101 mg, 75%) as a clear crystalline solid. MP: 91−92 °C; IR (Diamond cell, neat): 3263, 3203, 3157, 3055, 2968, 1570, 1507, 1384, 1312, 1263, 1107, 992, 831, 732, 538, 491, 463 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 7.09 (s, 1H), 6.91−6.72 (m, 4H), 5.86 (br. s, 1H), 3.72 (s, 3H), 1.84 (p, *J* = 6.8 Hz, 1H), 1.37 (s, 3H), 0.89 (dd, *J* = 15.1, 6.8 Hz, 6H), 1 NH not observed; ^{13}C NMR (75 MHz, chloroform-*d*) δ 138.6 (C), 136.5 (CH), 135.0 (C), 132.8 (C), 123.8 (CH), 122.1 (CH), 121.7 (CH), 118.1 (CH), 109.8 (C), 59.2 (C), 37.5 (CH), 34.6 (CH_3), 22.8 (CH_3), 18.8 (CH_3), 16.8 (CH_3); LRMS (+ESI) *m/z*: 257 (100, $[M + H]^+$) (40, $[M + Na]^+$); HRMS (+ESI) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{20}NaN_4$: 279.1580; found 279.1579.

*4-Cyclopentyl-1,4-dimethyl-1,4,5,10-tetrahydrobenzo[b]-pyrazolo[3,4-e][1,4]diazepine (**8d**).* Compound **2** was subjected to General Procedure B with 1-cyclopentylethan-1-one (65 μL, 0.62 mmoL) to afford **8d** (114 mg, 76%) as colorless needles. MP: 155−155 °C; IR (Diamond cell, neat): 2943, 2863, 1565, 1495, 1389, 1319, 1265, 986, 835, 729, 628 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 7.07 (s, 1H), 6.87−6.70 (m, 4H), 5.85 (br. s, 1H), 3.80 (br. s, 1H), 3.71 (s, 3H), 1.80 (d, *J* = 12.1 Hz, 1H), 1.69 (d, *J* = 11.1 Hz, 2H), 1.57 (d, *J* = 10.8 Hz, 2H), 1.37 (s, 4H), 1.12−0.92 (m, 5H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 138.7 (C), 136.0 (C), 135.6 (CH), 133.5 (C), 124.0 (CH), 122.3 (CH), 121.9 (CH), 118.1 (CH), 110.0 (C), 58.5 (C), 51.5 (CH), 34.7 (CH_3), 29.0 (CH_2), 26.8 (CH_3), 26.2 (CH_2), 26.0 (CH_2), 25.1 (CH_2); LRMS (+ESI) *m/z*: 283 (100, $[M + H]^+$), 305 (40, $[M + Na]^+$); HRMS (+ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{22}NaN_4$: 305.1737; found 305.1736.

*4-Cyclohexyl-1,4-dimethyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo-[3,4-e][1,4]diazepine (**8e**).* Compound **2** was subjected to General Procedure B with 1-cyclohexylethan-1-one (85 μL, 0.62 mmoL) to afford **8e** (126 mg, 80%) as a light needle-like solid. MP: 178−179 °C; IR (Diamond cell, neat): 3259, 2921, 1571, 1501, 1437, 1313, 991, 808, 750 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*) δ 7.07 (s, 1H), 6.87−6.70 (m, 4H), 5.87 (br. s, 1H), 3.80 (br. s, 1H), 3.71 (s, 3H), 1.80 (d, *J* = 12.1 Hz, 1H), 1.69 (d, *J* = 11.1 Hz, 2H), 1.57 (d, *J* = 10.8 Hz, 2H), 1.37 (s, 4H), 1.12−0.92 (m, 5H); ^{13}C NMR (126 MHz, chloroform-*d*) δ 138.6 (C), 136.7 (CH), 134.9 (C), 132.9 (C), 123.8 (CH), 122.0 (CH), 121.6 (CH), 118.1 (CH), 109.5 (C), 59.1 (C), 47.8 (CH), 34.6 (CH_3), 28.9 (CH_2), 27.1 (CH_3), 26.9 (CH_2), 26.6 (2 CH_2), 24.2 (CH_2); LRMS (+ESI) *m/z*: 297 (100, $[M + H]^+$); HRMS (+ESI) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{25}N_4$: 297.2074; found 297.2073.

*1-Methyl-5,10-dihydro-1H-spiro[benzo[b]pyrazolo[3,4-e][1,4]-diazepine-4,1′-cyclohexane] (**8f**).* Compound **2** was subjected to General Procedure B with cyclohexanone (64 μL, 0.62 mmoL) to afford **8f** (85 mg, 60%) as a chalk-like solid. MP: 190−191 °C; IR (Diamond cell, neat): 3301, 2920, 2849, 1565, 1489, 1431, 1389, 1312, 1267, 983, 901, 857, 751, 728, 713, 628 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 7.19 (s, 1H), 6.90−6.73 (m, 4H), 6.01 (br. s, 1H), 3.69 (s, 3H), 1.87−1.41 (m, 10H), 1 NH not observed; ^{13}C NMR (75 MHz, chloroform-*d*) δ 139.1 (C), 134.6 (CH), 134.5 (C), 134.1 (C), 124.1 (CH), 122.4 (CH), 121.6 (CH), 118.3 (CH), 112.2 (C), 54.8 (C), 38.1 (2 CH_2), 34.6 (CH_3), 25.1 (CH), 21.8 (2 CH_2); LRMS (+ESI) *m/z*: 269 (100, $[M + H]^+$); HRMS (+ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{20}NaN_4$: 291.1580; found 291.1580.

*1-Methyl-5,10-dihydro-1H-spiro[benzo[b]pyrazolo[3,4-e][1,4]-diazepine-4,1′-cyclopentane] (**8g**).* Compound **2** was subjected to General Procedure B with cyclopentanone (55 μL, 0.62 mmoL) to afford **8g** (78 mg, 60%) as a crystalline solid. MP: 146−147 °C; IR (Diamond cell, neat): 3256, 3200, 3156, 3051, 2949, 2870, 1567, 1499, 1436, 1311, 1265, 1207, 1002, 944, 730, 475 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 7.15 (s, 1H), 6.97−6.71 (m, 4H), 5.76 (br. s, 1H), 3.73 (s, 3H), 3.58 (br. s, 1H), 1.98−1.75 (m, 8H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 139.2 (C), 135.7 (C), 134.6 (CH), 134.4 (C), 124.3 (CH), 122.9 (CH), 121.9 (CH), 118.5 (CH), 109.4 (C), 64.7 (C), 41.2 (2 CH_2), 34.5 (CH_3), 23.3 (2 CH_2); LRMS (+ESI) *m/z*: 255 (100, $[M + H]^+$); HRMS (+ESI) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{18}NaN_4$: 277.1424; found 277.1423.

*4-(tert-Butyl)-1,4-dimethyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo-[3,4-e][1,4]diazepine (**8h**).* Compound **2** was subjected to General Procedure B with pinacolone (78 μL, 0.62 mmoL) to afford **8h** (57 mg, 40%) as a crystalline solid. MP: 142−143 °C; IR (Diamond cell, neat): 3298, 2980, 2953, 1570, 1493, 1390, 1315, 1267, 1108, 984, 858, 728, 708, 637 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 7.15 (s, 1H), 6.85−6.57 (m, 4H), 5.78 (br. s, 1H), 3.79 (br. s, 1H), 3.75 (s, 3H), 1.46 (s, 3H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 139.5 (C), 137.4 (C), 137.0 (CH), 131.64 (C), 122.06 (CH), 121.71 (CH), 120.96 (CH), 117.82 (CH), 106.8 (C) 62.14 (C), 41.69 (C), 34.7 (CH_3), 26.9 (3 CH_3), 26.3 (CH_3); LRMS (+ESI) *m/z*: 271 (100, $[M + H]^+$), 293 (20, $[M + Na]^+$); HRMS (+ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{22}NaN_4$: 293.1737 found 293.1736.

*1,4-Dimethyl-4-phenyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine (**8j**).* Compound **2** was subjected to General Procedure B with acetophenone (72 μL, 0.62 mmoL) to afford **8j** (54 mg, 35%) as a crystalline solid. MP: 115−116 °C; IR (Diamond cell, neat); 3267, 2965, 2155, 1562, 1490, 1432, 1370, 1312, 1263, 1192, 987, 836, 748, 699 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 7.32 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.22−7.10 (m, 1H), 6.99 (s, 1H), 6.86−6.74 (m, 1H), 6.77−6.65 (m, 2H), 6.65−6.54 (m, 1H), 5.87 (br. s, 1H), 4.00 (br. s, 1H), 3.75 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 147.4 (C), 139.3 (C), 136.8 (CH), 135.6 (C), 133.7 (C), 128.2 (2 CH), 127.0 (CH), 126.6 (2 CH), 124.6 (CH), 122.7 (CH), 122.0 (CH), 118.4 (CH), 109.6 (C), 59.9 (C), 34.7 (CH_3), 31.6 (CH_3); LRMS (+ESI) *m/z*: 291 (100, $[M + H]^+$); HRMS (+ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}N_4$: 291.1604; found 291.1603.

*1,4-Dimethyl-4-(4-nitrophenyl)-1,4,5,10-tetrahydrobenzo[b]-pyrazolo[3,4-e][1,4]diazepine (**8k**).* Compound **2** was subjected to General Procedure B with *p*-nitroacetophenone (102 mg, 0.62 mmoL) to afford **8k** (85 mg, 48%) as a crystalline solid. MP: 211−212 °C; IR (Diamond cell, neat): 3310, 1577, 1511, 1433, 1343, 1323, 1266, 1186, 1104, 990, 856, 823, 745, 699, 629 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 8.05 (d, *J* = 8.9 Hz, 2H), 7.43 (d, *J* = 8.9 Hz, 2H), 7.08 (s, 1H), 6.82 (m, 1H), 6.71 (m, 2H), 6.57 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.84 (br. s, 1H), 3.80 (s, 3H), 1.92 (s, 3H), 1 NH not observed; ^{13}C NMR (75 MHz, chloroform-*d*) δ 154.9 (C), 146.8 (C), 139.5 (C), 136.5 (CH), 134.8 (C), 133.7 (C), 127.6 (CH), 124.7 (CH), 123.5 (CH), 123.5 (CH), 122.4 (CH), 118.7 (CH), 108.0 (C), 60.1 (C), 34.8 (CH_3), 31.6 (CH_3); LRMS (+ESI) *m/z*: 358 (100, $[M + Na]^+$); HRMS (+ESI) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{17}NaN_5O_2$: 358.1275; found 358.1274.

*Dimethyl-2,2′-(1-methyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo-[3,4-e][1,4]diazepine-4,4-diyl)diacetate (**8m**).* Compound **2** was subjected to General Procedure B with dimethyl 3-oxopentanedioate (102 mg, 0.62 mmoL) to afford **8m** (139 mg, 76%) as a colorless crystalline solid. MP: 170−171 °C; IR (Diamond cell, neat): 3300, 2951, 1714, 1571, 1499, 1438, 1354, 1320, 1170, 987, 757 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 7.09 (s, 1H), 6.99−6.78 (m, 4H), 5.80 (br. s, 1H), 3.72 (s, 3H), 3.66 (s, 6H), 3.07 (d, *J* = 15.6 Hz, 2H), 2.89 (d, *J* = 15.6 Hz, 2H), 1 NH not observed; ^{13}C NMR (75 MHz, chloroform-*d*) δ 171.9 (2 C), 139.1 (C), 135.4 (C), 134.6 (CH), 134.4 (C), 124.9 (CH), 123.5 (CH), 122.5 (CH), 118.6 (CH), 106.9 (C), 56.2 (C), 51.7 (2 CH_3), 43.9 (2 CH_2), 34.6 (CH_3); LRMS (+ESI) *m/z*: 367 (100, $[M + Na]^+$); HRMS (+ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{20}NaN_4O_4$: 367.1377; found 367.1376

*Methyl-4-(bromomethyl)-1-methyl-1,4,5,10-tetrahydrobenzo[b]-pyrazolo[3,4-e][1,4]diazepine-4-carboxylate (**8n**).* Compound **2** was subjected to General Procedure B with methyl 3-bromo-2-oxopropanoate (66 μL, 0.62 mmoL) to afford **8n** (114 mg, 61%) as an unstable off-white solid. MP: >300 °C; IR (Diamond cell, neat): 3138, 2949, 2850, 1709, 1566, 1494, 1433, 1388, 1293, 1253, 1221, 1175, 1129, 1112, 980, 919, 891, 722 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*) δ 7.50 (s, 1H), 7.12−7.07 (m, 2H), 7.01−6.93 (m, 2H), 6.90 (s, 1H), 5.35 (s, 1H), 3.89−3.86 (m, 6H), 3.85 (d, *J* = 2.4 Hz, 1H), 3.41 (d, *J* = 10.3 Hz, 1H); ^{13}C NMR (126 MHz, chloroform-*d*) δ

DOI: 10.1021/acs.joc.6b00710
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170.6 (C), 141.9 (C), 135.3 (C), 134.1 (C), 132.8 (CH), 126.0 (CH), 124.3 (CH), 123.7 (CH), 119.7 (CH), 101.4 (C), 64.5 (CH_3), 53.5 (CH_2), 52.9 (C), 39.9 (CH_3); LRMS (+ESI) *m/z*: 351/353 (100, $[M + H]^+$); HRMS (+ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{16}BrN_4O_2$: 351.0451/353.0431; found 351.0456/353.0436.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00710.

^1H and ^{13}C NMR spectra for compounds **2**, **7a−j**, **8a−h**, **8j−k**, and **8m−n** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Australian National Health and Medical Research Council.

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DOI: 10.1021/acs.joc.6b00710
J. Org. Chem. 2016, 81, 4883−4889